

INTRODUCTION

- Neurofibromatosis type 1 (NF1) is an inherited tumor syndrome caused by heterozygous germline mutations in the NF1 gene, occurring in approximately 1/2600 individuals.²
- A subset of patients with neurofibromatosis type 1 (NF1) develop juvenile xanthogranulomas (JXGs), a non-Langerhans cell histiocytosis, and some of these patients also develop juvenile myelomonocytic leukemia (JMML). Yet, these associations are poorly delineated.
- JXG is a benign proliferation of non-Langerhans cells histiocytes characterized by small yellow/brown papulonodules ranging from 1-20 mm in size.³
- JMML is a mixed myeloproliferative-myelodysplastic disorder that affects children, most often before age 6.⁴
- The first and only systematic review on this described the risk of developing JMML 20 to 30 times higher in patients with NF1 with JXG lesions compared to those without JXG.¹
- Since then, mostly isolated case reports have either refuted or confirmed this triple association.

AIMS

Our objectives in performing this systematic review are to: (1) **clarify the relationship between NF1, JXGs, and JMML** and **identify patients that may benefit from additional screening**, and (2) describe the **clinical characteristics of JXGs arising in NF1**.

METHODS

- Articles were included if they were peer-reviewed human studies, in English, and discussed one or more association between NF1, JXG, and/or JMML with individual patient data
- Articles were screened according to Figure 1.
- Included: 65 articles, 181 individual patients
- Patients were grouped (1-4) by association:

Groups (Dx)	No. of patients
1 (NF1 and JXG)	56
2 (NF1 and leukemia)	98
3 (NF1, JXG, and leukemia)	18
4 (JXG and leukemia)	9

RESULTS

Groups	Sex, n (%)		Median age (yrs), (range)					FHx, n (%)		
	Males	M-F ratio	Presentation	Leukemia dx	JMML dx	JXG onset	Follow up	FHx of NF1	Maternal NF1 transmission	M-P ratio
1	19 (54.3)	1.2:1	1.5 (0-28)	-	-	1.5 (0.21-23)	4 (0-10)	9 (31.0)	6 (75.0)	3
2	63 (66.3)	2.0:1	3.7 (0.2-75)	3.5 (0.1-75)	2.5 (0.2-7)	-	3 (0-17.8)	33 (61.1)	19 (61.3)	1.9
3	14 (93.3)	14:1	0.8 (0-0.8)	1.8 (0.3-7.5)	1.8 (0.3-4.5)	0.8 (0.1- 4.4)	3 (0.2-7.9)	8 (66.7)	4 (57.1)	1.3
4	5 (55.6)	1.3:1	2 (0.1-23)	2.5 (0.5-68)	2.2 (0.5-2.5)	1 (0.1-65)	1.3 (0.9-3.5)	0 (0.0)	0 (0.0)	-

Table 1. Patient characteristics.

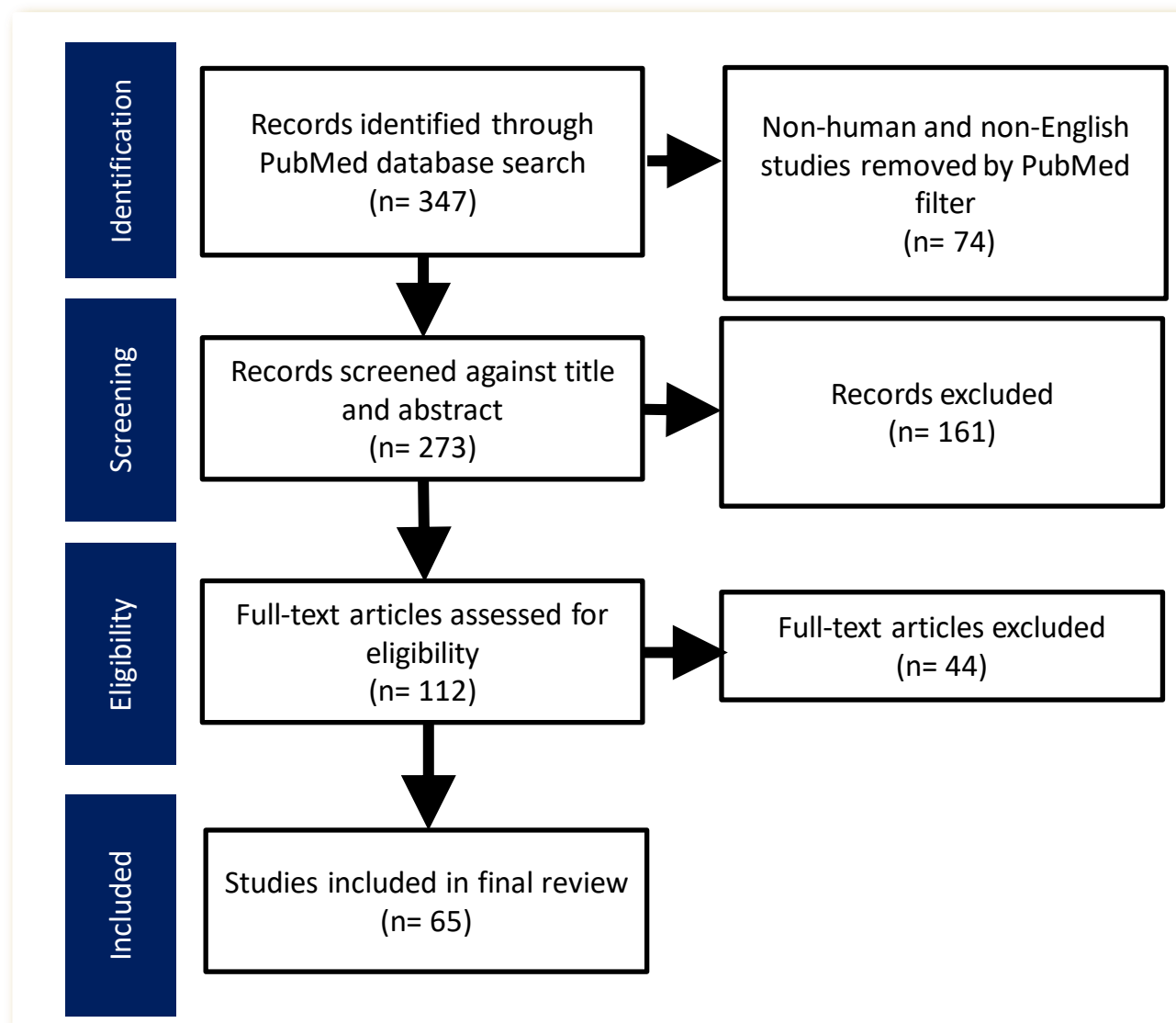


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) flow diagram.

GROUP 3: TRIPLE ASSOCIATION

- Among the 78 patients with NF1 and JXG, **23% (18/78) developed leukemia**, and more specifically, **19% (15/78) developed JMML**, which is more than what has been reported in NF1 patients alone.
- Significant **male predominance** (93%), Table 1
- Majority of patients had a **family history of NF1** (67%)
- JMML is the most common subtype (83%) compared to other groups
- Earlier onset of JXGs (0.8 years) and leukemia (1.8 years), Table 1
- JXGs precede onset of leukemia and JMML
- Majority of pts had multiple JXGs, regardless of Group
- JXGs had a predilection for the face, scalp and neck in all groups, as well as the trunk in Group 3

Table 2. Leukemia subtypes by groups. While JMML makes up majority of leukemia cases across all groups, this was most significant in Group 3, $p = 0.0172$.

Subtype	Group 2	Group 3	Group 4
JMML	43% (42/98)	83% (15/18)	55% (5/9)
AML	18% (18/98)	5% (1/18)	11% (1/9)
ALL	16% (16/18)	-	22% (2/9)
CML	11% (11/98)	11% (2/18)	-
ATLL	-	-	11% (1/9)
CEL	1% (1/98)	-	-
NM	10% (10/98)	-	-
Total	98	18	9

Table 3. Size and number of JXG lesions between groups. Group 4 had significantly more lesions. Majority of patients had multiple lesions regardless of leukemia or NF1 diagnosis, and there was no significant difference in the number of lesions.

Groups	JXG lesions, median (cm), (range)		n (%)
	Size	Number	
1	0.3 (0.3-1.5)	2.9 (1-50)	48 (90.6)
2	-	-	-
3	0.5 (0.2-0.6)	6.5 (1-100)	13 (86.7)
4	0.6 (0.4-1.3)	26 (1-100)	6 (85.7)
p-value	0.43	0.013*	0.89

Table 4. Location of JXG lesions between groups. JXGs were most commonly located on the face, neck, and scalp in all groups, but also the trunk in Group 3 and the lower extremities in Group 4.

Location	1		3		4	
	N	%	N	%	N	%
Face	24	70.6	8	61.5	5	62.5
Scalp/neck	26	76.5	11	84.6	8	100
Trunk	15	44.1	9	69.2	4	50
Upper extremities	9	26.5	1	7.7	4	50
Lower extremities	6	17.6	3	23.1	5	62.5
Eyes	2	5.9	1	7.7	0	0
Genitals	0	0	0	0	0	0
Cerebello-pontine angle	1	2.9	0	0	0	0
TOTAL	34	100	13	100	8	100

LIMITATIONS

- Possible underdiagnoses of the triple association as most JXG lesions regress, potentially before they are diagnosed or the onset of leukemia and/or NF1
- Length of follow up possibly not long enough for leukemia onset
- Small size of groups 3 and 4
- Our observed frequencies of leukemia and JMML are likely inflated due to publication bias. Meaning our calculations are based on published studies, which are those that are rare and unlikely to represent the general population.

CONCLUSIONS

- Our findings suggest that the NF1 patients with JXGs have an increased risk of developing JMML and leukemia, especially in males with a family history of NF1.
- The onset of JXGs, leukemia, and JMML tended to occur at earlier ages in those with the triple association compared to other groups. After age 6, the risk of developing JMML continues to decline with age. Thus, screening at an early age might be beneficial.
- Currently, there are no guidelines specifically for pts with NF1 and JXGs
- Although the triple association remains rare, **closer surveillance and screening of male patients with familial NF1 and JXGs lesions may be reasonable, particularly at early ages.**

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