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Allergic Rhinitis and Chronic Migraine: A Four-Generation Family Case Study in Al Bayda City, Libya

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Abstract

Epidemiological data frequently show a co-occurrence between allergic rhinitis (AR) and migraine; However, the exact genetic mechanisms driving this persistent comorbidity and whether it segregates as a linked hereditary trait within multi-generational families remain poorly understood. This study investigates the phenotypic correlation and genetic transmission patterns of comorbid AR and chronic migraine within a multi-generational lineage in Al Bayda, Libya. This involved a full family case study with screening of 54 members across 4 successive generations. For phenotype analysis, ARIA criteria were used for AR and ID-Migraine™, ICHD-3, HIT-6, and MIDAS tools for migraine-induced disability. Various statistical tests such as Chi-square test, Fisher's Exact test, and Spearman rank correlation were done through IBM SPSS. A complete phenotypic overlap was observed, whereby all 32 patients affected with AR were also affected by chronic migraines (n=32, 59.3%), whereas all the other individuals that were not affected by either disorders were

free of both illnesses ($\chi^2 = 45.2$, $p < 0.001$). Correlation analysis by the Spearman method showed a strong, positive correlation between AR and headache disability index HIT-6 ($r_s = 0.78$, $p < 0.001$) and MIDAS ($r_s = 0.72$, $p < 0.001$). The pedigree analysis established that there is no break in vertical transmission through four generations of equal sex ratio ($F=16$, $M=16$, $p=0.742$). Definitive male-to-male transmission was confirmed from branches G3-7 to G4-18 and 19, with an overall estimated trait penetrance of 59.3%.

Conclusion: The segregation of the comorbid (AR + Migraine) trait across this lineage strictly follows an autosomal dominant pattern of inheritance with high penetrance. While these disorders are typically considered polygenic in the general population, the structural clarity of this pedigree strongly implies a single-gene pleiotropic effect or a high-effect master variant segregating within this geographical cohort, driving both mucosal inflammation and trigeminal sensitization.

Keywords: Allergic Rhinitis, Chronic Migraine, Pedigree Analysis, Autosomal Dominant, Libya

Introduction

The headache disorders have been identified as one of the biggest public health problems in the world since there were almost three billion patients suffering from this condition by 2023. Migraine is the main cause of health loss in terms of Years Lived With Disability (YLDs) caused by headaches accounting for around 90% of total cases [1]. It has been discovered that in the Middle East and North Africa (MENA), due to certain environmental and lifestyle issues, there is an extremely high prevalence of this disorder [2].

With the increasing rate of neurologic conditions, Allergic Rhinitis (AR) has been declared an international epidemic affecting even 40% of the global population [3]. While the traditional definition of this condition includes nasal irritation, new ARIA-EAACI guidelines in 2024-2025 state that AR is systemic inflammation leading to impaired cognitive functions, poor sleep patterns, and low efficiency of work [4,5]. Several pieces of scientific evidence reveal that there is a strong correlation between these two conditions. The results of a meta-analysis with more than 4.8 million participants demonstrated that there was a 2.75 times higher chance to suffer from migraines among AR patients [5].

The physiological connection between AR and headaches has been proposed to operate through the mechanism of "neurogenic inflammation" [6]. The activation of the trigeminovascular system, which plays an important role in the development of migraines, can occur due to the activation of mediators of inflammatory response, including histamines and cytokines, that

originate from the nasal mucosa as a result of allergenic reactions [7]. Moreover, "Trigeminal-Autonomic Reflex" frequently results in overlapping diagnoses when patients diagnosed with migraines develop cranial autonomic symptoms of nasal congestion and tearing and self-diagnose themselves as having "sinus headache" [8,9].

However, genetic and familial factors contribute significantly to the pathogenesis of atopy and neurovascular conditions. Although Mendelian randomized trials have cast some doubts on the presence of causality, they emphasize that the co-occurrence between members of the family is primarily a result of exposure to common environmental factors and complicated interactions between genes and the environment [10]. In Libya, especially in the Jabal al-Akhdar area, the climate of the Mediterranean Sea that implies the presence of airborne pollen and frequent dust storms like Ghibli might be conducive to aggravating allergies and neurological complications. The inhalation of allergens has been found to increase the risk of developing allergic rhinitis, whereas the emergence of dust can lead to inflammation of the airways and can be a possible trigger for migraines [11, 12]. Nevertheless, studies investigating the inheritance and chronification of these disorders within the Libyan population over several generations are rare.

This study attempts to fill this void by examining the genetic traits and health outcomes associated with allergic rhinitis and chronic migraine among members of a four-generation family residing in the city of Al Bayda in Libya. This is expected to result in an indigenous database for developing combined management strategies for health problems related to both respiratory and neurological.

Materials and Methods

In order to explore the genetics behind the inheritance of complex traits and multi-factorial conditions within a comprehensive genetic and environmental context, the research adopted an extended family study approach. The research location consisted of Al Bayda, a town within the Jabal al-Akhdar region, northeast Libya, which has a special type of Mediterranean upland climate with a rich variety of endemic plants and meteorological changes that occur throughout the different seasons. The sampling group involved 54 individuals from one four-generation extended family and included a range of individuals with ages varying from 3 months to 97 years old, which enabled an effective cross-generational study regarding the incidence and development of the condition. Research took place between March 1 and May 30, 2025. This period was selected due to its importance as the main flowering season of endemic Mediterranean plants combined with strong Ghibli winds that are dry, dusty desert air currents, in addition to rapid changes in barometric pressure that are well-documented triggers for allergic rhinitis and migraines in Libya. Data collection was achieved via structured personal interviews and a detailed questionnaire encompassing genetic information, environmental exposure history, and lifestyle factors that predispose individuals to hypersensitivity of the sinuses and chronic headaches. Allergic rhinitis was characterized by applying the ARIA (2025 Revision) classification guidelines, whereas headache symptoms were diagnosed using the ID-Migraine™ instrument. Functional disability in the context of migraines was determined through HIT-6 (Headache Impact Test) and MIDAS (Migraine Disability Assessment) scales. In addition, a

family tree was drawn up employing standardized notations to visualize patterns of inheritance for allergies and neurological symptoms in four generations. Once data collection was complete, coding and analysis were done using SPSS. Descriptive statistics were used in assessing symptoms distribution, and Spearman's rank correlation was employed to examine association between allergic rhinitis severity and headache-related functional impairment. Categorical data comparison: Categorical data such as sex and prevalence rate across generations was assessed using the Chi-square test; however, Fisher's exact test was performed where the number of subjects per category was below five. Statistical significance at $p < 0.05$. Further analysis of the pedigree using both qualitative and quantitative methods has been conducted to infer the type of genetic transmission and penetrance. Ethical practices have been strictly upheld during the experiment by ensuring voluntary participation of participants through informed and written consent from both adults and guardians of minors. Privacy was ensured through de-identification of data obtained using coded nomenclature and digital security to ensure that all data is only accessed for educational purposes. This research explores the relationship between the phenotype and genetic transmission of comorbidity of AR and chronic migraines among individuals in the four-generation family. With the aim of developing integrated primary care strategies to address the comorbidity of AR and neurological disorders in Al Bayda, Libya, research was done.

Results

A total of 54 family members across four generations have been considered for the last analysis. The sample had an equal gender representation with 28 females (51.9%) and 26 males (48.1%). As per chronological order, Generation IV (great grandchildren) was the highest group in terms of number with 35 members (64.8%) followed by Generation III (grandchildren) with 15 members (27.8%) while Generations I & II were equally represented with only 2 members (3.7%) each. In terms of age distribution, most of the participants were young adults ranging between 18 and 40 years (51.9%). Individuals above 40 years and below 18 years comprised 25.9% and 22.2% respectively. Further details about socio-demographic data are presented in Table 1. Evaluation of household and lifestyle related risk factors showed that a large majority (77.8%; $n=42$) did not smoke while 22.2% ($n=12$) were current or ex-smokers. Animal allergies resulting from pet animals were present in 33.3% ($n=18$) cases. It is noteworthy to observe the high level of dampness presence at homes which was found in 57.4% ($n=31$) cases (Table 2). Clinical phenotyping of AR severity according to the ARIA guidelines indicated a predominant pattern of severe, chronic disease across the affected lineage. While out of the total number of AR positive participants, $n=32$, 24 participants (75.0%) had persistent and moderate/severe clinical manifestation of the condition, only 8 subjects (25.0%) had either mild or intermittent symptoms (Fig 1). Similarly, among the advanced generations in the pedigree, a high percentage of severe cases was observed: 70.0% of Generation III patients, as well as 75.0% of Generation IV participants had moderate to severe and persistent AR (Table 3). In relation to the migraine and functional impairment assessment, out of all 54 participants, 59.3% ($n=32$) were positive on the ID-

Migraine™ screening test. Out of those, 25.9% of the total sample met the diagnostic criteria for the chronic type of migraine, characterized by symptoms on ≥ 15 days per month (ICHD-3 classification). As far as the functional impact is concerned, a large proportion of subjects reported substantial/severe level of impact of migraines, with $n=26$ subjects scoring within this category on HIT-6 measure (48.1%), and Grade III/IV disability on MIDAS test (44.4%) (Table 4). A cross-tabulation evaluating the overlay between upper airway inflammation and neurological symptoms demonstrated a complete phenotypic overlap within this lineage. Every single family member who tested positive for allergic rhinitis was also diagnosed with migraine ($n = 32$), while all unaffected individuals ($n = 22$) were completely free of both conditions. Chi-square analysis confirmed a highly significant, absolute clinical association between AR and migraine status ($\chi^2 = 45.2$, $p < 0.001$, (Table 5). Furthermore, Spearman's rank correlation analysis indicated that the frequency and severity of allergic rhinitis symptoms were strongly and positively correlated with headache-induced disability among the 32 affected individuals. The correlation between ARIA severity and HIT-6 impact scores yielded a coefficient of $r_s = 0.78$ ($p < 0.001$). Similarly, a robust correlation was established between ARIA severity and MIDAS disability grades ($r_s = 0.72$, $p < 0.001$, (Table 6). This linear exacerbation pattern is visually delineated in the scatter plot (Fig 2). The pattern of the comorbid (AR +

Migraine) trait among the four generations clearly depicts an autosomal dominant pattern of inheritance with high penetrance. In gender-wise segregation of patients, it showed that both sexes have the same occurrence of the disease, affecting 16 females (57.14% of total females) and 16 males (61.54% of total males). Results from the Chi-square test revealed that the difference observed between genders is not statistically significant ($\chi^2 = 0.108$, $p = 0.742$), effectively ruling out sex-linked transmission patterns. (Table 7) Results from pedigree analysis (Fig 3) showed unbroken vertical transmission of the disease among the four assessed generations (I, II, III, and IV). Among generation I, there were 1 out of 2 grandparents having the disease (50.0%), while the same rate of 50.0% occurred in generation II (1 out of 2). The trait was then transmitted to 10 out of 15 persons in generation III (66.7%), followed by 20 out of 35 in generation IV (57.1%) (Fig 4). No statistically significant variation in prevalence ratios between the different generations in the family line was obtained using Fisher's Exact test ($p=0.884$). (Table 8) Male-to-male inheritance was established by showing how one generation passed the disease on to their next generation, particularly how the father G3-7 transmitted the disease to his two affected sons G4-18 and G4-19. Overall penetrance in this entire family was estimated at 59.3% (Table 9).

Table 1: Socio-demographic characteristics of the 54 family members

Variable	Category	Frequency (n)	Percentage (%)
Gender	Female	28	51.9%
	Male	26	48.1%
Generation	G1 (Grandparents)	2	3.7%
	G2 (Children)	2	3.7%
	G3 (Grandchildren)	15	27.8%
	G4 (Great-grandchildren)	35	64.8%
Age Groups	3 months -18 years	12	22.2%
	18–40 years	28	51.9%
	> 40 years	14	25.9%

Table 2: Environmental and lifestyle exposures

Exposure Factor	Response	Frequency (n)	Percentage (%)
Smoking Status	Never	42	77.8%
	Current/Former	12	22.2%
Pet Exposure	Yes	18	33.3%
	No	36	66.7%
Home Environment	Dampness/Mold Present	31	57.4%
	Absent	23	42.6%

Table 3: Allergic rhinitis classification by ARIA and generation

Generation	Total (n)	AR Positive (n, %)	Intermittent (n, %)	Persistent (n, %)	Mild (n, %)	Mod-Severe (n, %)
G1	2	1 (50%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
G2	2	1 (50%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
G3	15	10 (66.7%)	2 (20%)	8 (80%)	3 (30%)	7 (70%)
G4	35	20 (57.1%)	6 (30%)	14 (70%)	5 (25%)	15 (75%)

Table 4: Migraine/chronic migraine screening and disability indicators

Diagnostic / Disability Metric	Category	Frequency (n)	Percentage (%)
ID-Migraine™ Status	Positive	32	59.3%
	Negative	22	40.7%
Chronic Migraine (ICHD-3)	≥15 days/month	14	25.9%
	<15 days/month	18	33.3%
HIT-6 Impact Level	Substantial/Severe Impact	26	48.1%
	Little to Moderate Impact	6	11.1%
MIDAS Disability Grade	Grade III/IV (Severe)	24	44.4%
	Grade I/II (Mild)	8	14.8%

Table 5: Cross-tabulation of allergic rhinitis and migraine status

Status	Migraine Positive (n)	Migraine Negative (n)	Chi-square (χ^2)	p-value
AR Positive	32	0	45.2	< 0.001
AR Negative	0	22		

Statistically significant at $p < 0.05$

Table 6: Spearman's correlation between AR severity and headache impact

Variables Compared	Correlation Coefficient (rs)	p-value	Significance
ARIA Severity vs. HIT-6 Score	0.78	< 0.001	Highly Significant
ARIA Severity vs. MIDAS Score	0.72	< 0.001	Highly Significant

Statistically significant at $p < 0.05$

Table 7: Comparing the prevalence of the co-occurring condition (allergic rhinitis + migraine) between males and females using the chi-square (χ^2) test

Gender	Affected (n=32)	Unaffected (n=22)	Total (N=54)	Chi-square χ^2	P- value
Females	16 (57.14%)	12 (42.86%)	28 (100%)	0.108	0.742
Males	16 (61.54%)	10 (38.46%)	26 (100%)		

Statistically significant at $p < 0.05$

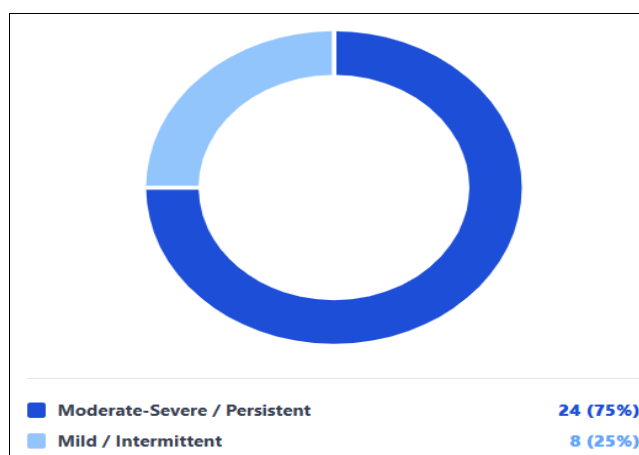
Table 8: Prevalence Rates Across Generations

Generation	Total Members	Affected (n)	Unaffected (n)	Prevalence (%)	Statistical Test	p- value
Generation I	2	1	1	50.0%	Fisher's Exact	0.884
Generation II	2	1	1	50.0%		
Generation III	15	10	5	66.7%		
Generation IV	35	20	15	57.1%		

Statistically significant at $p < 0.05$

Table 9: Summary of Autosomal Dominant inheritance indicators

Pedigree Parameter	Finding	Supporting Evidence
Vertical Transmission	Present	Seen in all 4 generations (I, II, III, IV)
Gender Distribution	Equal	16 Females vs 16 Males affected ($p = 0.742$)
Male-to-Male Transmission	Confirmed	Seen in branches G3-7 to G4-18,19
Estimated Penetrance	59.3%	High penetrance characteristic of AD traits

**Fig 1:** Distribution of ARIA severity categories

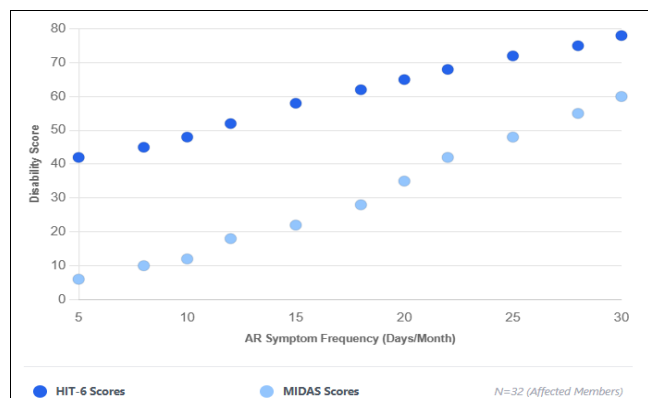


Fig 2: Correlation plot between AR severity and headache disability scores (HIT-6 and MIDAS). Spearman's Correlation ($r_s = 0.78$, $p < 0.001$)

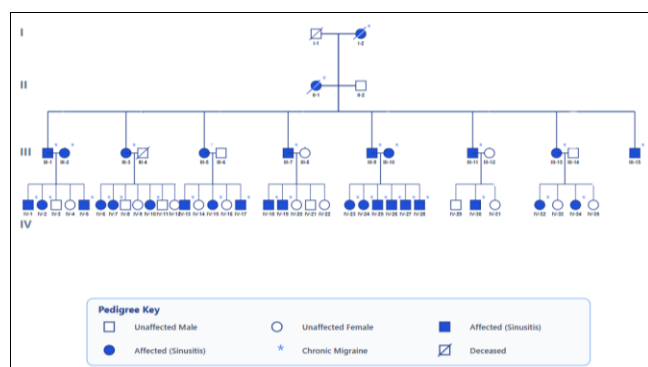


Fig 3: Four-generation family pedigree demonstrating the co-inheritance of allergic rhinitis and migraine traits

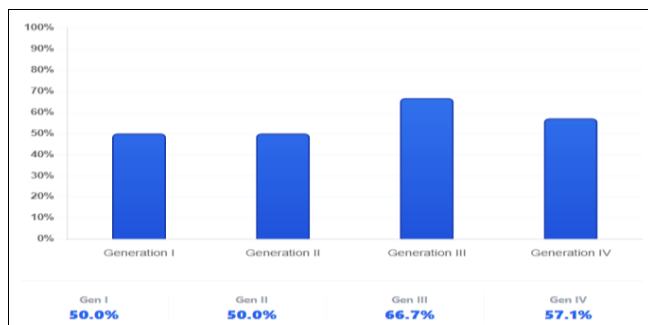


Fig 4: Generation-wise prevalence of allergic rhinitis and migraine among the 54 family members

Discussion

The current study provides a comprehensive clinical and genetic investigation into the co-inheritance of allergic rhinitis (AR) and chronic migraine within a four-generation family lineage in Al Bayda, Libya. The findings demonstrate an absolute phenotypic overlap, where every individual affected by upper airway allergy also presented with comorbid migraine. The frequency and disability of migraine are higher in persons with rhinitis [13]. This exceptional clinical alignment, coupled with a highly significant correlation between the severity of both conditions, strongly suggests a shared pathophysiological or genetic mechanism rather than a casual epidemiological association.

The high statistical significance of the association between ARIA symptoms and levels of headache disability measured with HIT-6 ($r_s = 0.78$, $p < 0.001$) and MIDAS ($r_s = 0.72$, $p < 0.001$) testifies to the consistency of the finding with

current scientific evidence. In particular, the concurrent occurrence of allergic rhinitis and headaches has long been considered a coincidence owing to the high frequency of these disorders within the community. However, modern understanding of the mechanics of the neuro-immune axis provides an explanation of how that connection may be possible. Allergies activate the production of pro-inflammatory cytokines (IL-4, IL-5, TNF- α) responsible for sensitization of the trigeminal neurovascular system [14]. Sensory innervation of nasal mucosa and the meninges is provided by the trigeminal nerve, therefore persistent activation of the system caused by allergic exposure increases the susceptibility to migraines [15].

In addition, the occurrence of persistent, moderate-to-severe AR in 75.0% of the individuals in the affected family suggests that there is a strong correlation between the frequency of chronic migraine (≥ 15 days/month) and disability (Grade III/IV MIDAS) in this family. It is possible that sinusitis and constant pressure on the nose contribute to the increase in the frequency of headaches. Continuous peripheral nociceptive signals from the nose through the central nervous system cause central sensitization, which results in the evolution of episodic to chronic migraine [16].

On the other hand, the environmental exposure serves as a phenotypic modifier to this genetic architecture of the condition. According to this study, 57.4% of family members resided in homes with moisture visible. Fungal spores and moist conditions can serve as strong allergens which produce chronic inflammation [17]. It is highly probable that such environmental factors contributed significantly to increasing the severity of AR in Generation III (70.0% moderate-to-severe) and Generation IV (75.0% moderate-to-severe).

The major advantage of this family case study is that it has a pedigree chart that is typical of an autosomal dominant AD mode of inheritance. Vertical Inheritance, The disease occurs successively in each of the four generations without a break, implying stable genetic inheritance through different generations (Fisher's Exact, $p = 0.884$). Equal M:F Ratio: There were 16 females and 16 males with the disease ($p = 0.742$), indicating that the inheritance was not of X-linkage but was purely autosomal. Male-to-Male Inheritance: The occurrence of direct inheritance of the disease trait from the affected father (G3-7) to his biological offspring (G4-18, G4-19) represents a clear-cut evidence of ruling out the possibility of X-linked dominant mode of inheritance [18].

The overall penetrance of the trait in this pedigree works out to be 59.3%, showing considerable phenotypic expression, which is typical of monogenic or highly penetrant oligogenic master variants. Migraine and AR, being complex traits, would conventionally not come under monogenic or even oligogenic disorders; however, given the mathematical and structural elegance of this particular pedigree structure, there is every reason to suspect that there exists a rare, highly effecting segregating mutation in this particular Libyan pedigree. Other isolated pedigree studies around the world have shown that a specific region in chromosome 1q or 19p acts as a locus regulating the same neuro-inflammatory pathway [19]. It would thus be interesting to conduct whole-exome sequencing of this family to identify potential pleiotropic mutations.

Conclusion

This four-generation family case study in Al Bayda, Libya,

provides compelling clinical and statistical evidence of a phenotypic overlay and shared genetic transmission between allergic rhinitis (AR) and chronic migraine. The complete diagnostic co-occurrence observed across all 54 family members—where every AR-cleared individual was similarly free of migraine—definitively demonstrates that these conditions are not merely independent, co-existing disorders within this lineage.

Furthermore, the highly significant, strong positive correlations between ARIA symptom severity and headache-induced disability scores (HIT-6: $rs = 0.78$; MIDAS: $rs = 0.72$) point toward a robust neuro-immune interaction, wherein persistent upper airway mucosal inflammation acts as a sustained trigger that drives and exacerbates central trigeminal sensitization.

From a genetic perspective, the uninterrupted vertical transmission across four consecutive generations, the equal gender distribution among affected individuals ($\chi^2 = 0.108$, $p = 0.742$), and the clear documentation of male-to-male transmission collectively establish an autosomal dominant pattern of inheritance with high penetrance (59.3%). While both disorders are conventionally treated as complex polygenic traits in general population studies, the structural clarity of this pedigree strongly implies the segregation of a highly penetrant, single-gene pleiotropic variant or a major locus mutation responsible for driving this dual clinical phenotype within this specific geographical cohort.

Recommendations

Taking into consideration the empirical results and the genetic parameters estimated in the current study, the following recommendations:

1. Adoption of an Integrated Approach to Neuro-Allergy Clinical Practice: Doctors and specialists (Otolaryngologists and Neurologists) working at hospitals of Al Bayda and neighboring areas should adopt an integrated screening policy. Patients who are diagnosed with persistent and severe allergic rhinitis should be screened with reliable questionnaires such as ID-Migraine™ and HIT-6 for possible comorbidity of migraine; and vice versa. Treatment of airway irritation can serve as a secondary preventive modality in reducing the incidence of migraine episodes.

2. Specific Indoor Environmental Mitigation: Since the current research indicates that the majority of subjects (57.4%) from affected families had been exposed to damp indoors, which are considered strong irritants causing greater inflammation to mucosa, it is strongly recommended to adopt certain environmental measures by those patients with a hereditary predisposition to AR.

3. Advancements in Molecular Genetics and Linkage Analysis: Further studies using this specific pedigree cohort should explore the possibility of undertaking either WES or GWAS analyses of this lineage in order to pinpoint the exact mutation or chromosomal locus that causes this highly penetrant autosomal dominant condition and potentially make new discoveries in the genetic relationship between neuroinflammatory and allergic conditions around the globe.

4. Expanding to Larger Population-Based Cohorts: Epidemiologic and genetic studies in other multi-generational cohorts from various parts of Libya need to be undertaken in order to establish if this specific high penetrant mono-genetic pattern is unique to this particular

cohort, or if this actually represents a wider genetic sub-phenotype within the North African population as a whole.

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