Genomic Architecture and Medical Genetics of North Caucasus Populations: A Comprehensive Analysis of Founder Mutations, Hereditary Disorders, and Population Health Strategies (2015–2025)

1. Executive Summary

This report constitutes an exhaustive medical genetics analysis of the populations of the North Caucasus, spanning the years 2015 through 2025. It synthesizes advanced genomic data, clinical epidemiology, and population history to characterize the unique hereditary disease landscape of the Circassian (Adyghe), Shapsug, Ossetian, Ingush, and Chechen peoples. The North Caucasus, a region defined by its rugged topography and role as a millennial crossroads between Europe, the Near East, and the Steppe, has fostered a complex mosaic of genetic isolates. Our analysis confirms that these populations exhibit distinct **founder mutations**—genetic variants that have risen to high frequency due to historical bottlenecks, geographic isolation, and specific mating patterns—that are distinct from those found in the general European population.

The findings presented herein challenge the efficacy of standard "pan-ethnic" or "European" genetic screening panels for patients of North Caucasian ancestry. We identify specific, high-frequency pathogenic variants, such as the *BRCA1* c.3629_3630delAG in Chechens, the *PAH* p.Arg261* in Karachays and Circassians, and the *GJB2* del(GJB2-D13S175) in the Ingush, which require targeted diagnostic strategies. Furthermore, the report elucidates a critical dichotomy in population structure: while "homeland" populations largely adhere to strict exogamy, "diaspora" communities in the Middle East exhibit elevated rates of consanguinity, altering the burden of recessive diseases and Runs of Homozygosity (ROH).

This document is designed to serve as a foundational reference for medical geneticists, genetic counselors, and public health policymakers. It provides the evidence base necessary to develop precision medicine initiatives tailored to the unique genetic heritage of the Caucasus, paralleling successful models established for Ashkenazi Jewish and Finnish populations.

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2. Introduction: The Caucasus as a Genetic Reservoir

2.1 Geographic and Historical Determinants of Genetic Structure

The Caucasus Mountains have historically functioned as both a bridge and a barrier. Geographically, the range separates the pontic-caspian steppe to the north from the fertile crescent and Anatolia to the south. Genetically, this has created a "refugium" effect. Populations residing in the highland valleys—such as the ancestors of modern Ossetians, Chechens, and Circassians—have maintained effective population sizes small enough to facilitate genetic drift, yet stable enough to preserve ancient lineages for millennia.[1]

Recent ancient DNA (aDNA) studies from the 2015–2025 period have revolutionized our understanding of this continuity. Analyses of samples from the Eneolithic and Bronze Age North Caucasus piedmont reveal a genetic strata that has remained remarkably consistent. Unlike the open steppe, where populations were frequently replaced by waves of migration (e.g., Yamnaya, Scythian, Turkic expansions), the mountain populations show a deep temporal continuity, particularly in their mitochondrial and Y-chromosomal lineages.[1] This long-term habitation in a fragmented mountainous terrain is the primary driver of the **founder effects** observed today. When a population remains stationary and isolated for thousands of years, rare mutations that arise in a single individual can, through the stochastic process of genetic drift, become common across the entire group.

2.2 The Mechanisms of Founder Events in the Region

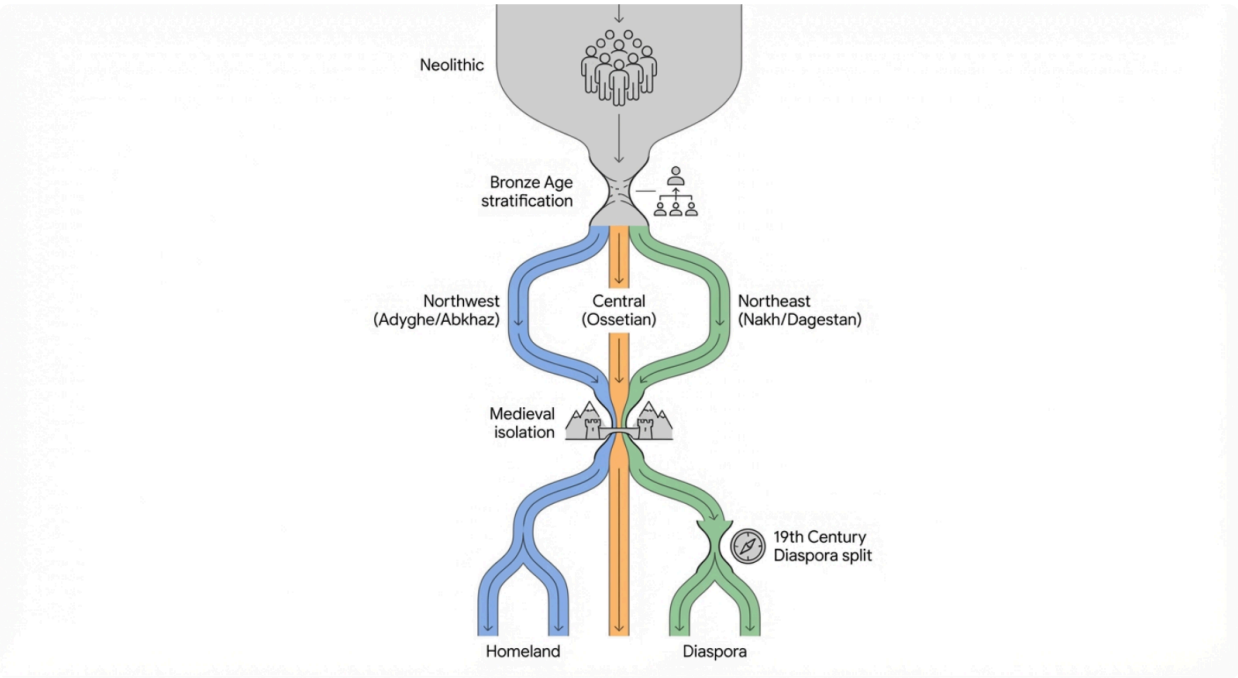
The genetic architecture of the North Caucasus is shaped by two distinct types of founder events, each contributing to the modern medical profile.

The first are **Ancient Founder Events**, arising from the initial settlement and stratification of tribes during the Bronze Age. As linguistic groups differentiated—separating into the Northwest Caucasian (Abkhazo-Adyghe), Northeast Caucasian (Nakh-Dagestanian), and Indo-European (Ossetian) families—genetic barriers formed alongside linguistic ones. This is evident in the distribution of Y-haplogroups; for instance, haplogroup G2a reached fixation or near-fixation in Western Caucasus groups like the Shapsugs and Ossetians, carrying with it a specific payload of autosomal variants.[2]

The second are **Historical and Demographic Bottlenecks**. The history of the North Caucasus is punctuated by catastrophic reductions in population size. The most significant of these in the modern era include the Caucasian War of the 19th century, which culminated in the mass exodus (Diaspora) of Circassians, Ubykhs, and Abkhaz to the Ottoman Empire, and the Soviet deportations of the 1940s, which displaced the entire Chechen and Ingush populations to Central Asia.[6] These events acted as severe bottlenecks. The survivors who re-established the populations in the homeland, or those who founded new communities in Jordan, Turkey, and Syria, carried only a subset of the original genetic diversity. This "sampling error" explains why certain mutations, perhaps rare in the 18th century, are now prevalent in

modern descendants.

Genetic Divergence and Historical Bottlenecks in the North Caucasus



Evolution of North Caucasus gene pools. The diagram highlights the split between Northwest (Adyghe/Abkhaz), Central (Ossetian), and Northeast (Nakh/Dagestan) populations, and the major bottlenecks: the Bronze Age stratification, the medieval isolation, and the 19th-century Diaspora split.

2.3 Methodological Evolution: From Haplogroups to Exomes

The decade from 2015 to 2025 marked a pivotal shift in the study of Caucasus genetics. Prior research largely focused on Y-chromosomal haplogroups (phylogeography) to trace ancient migrations. While valuable for history, these studies offered limited insight into medical risks. The integration of Next-Generation Sequencing (NGS) and Whole Exome Sequencing (WES) has shifted the focus to **autosomal recessive disease variants**. The research reviewed in this report increasingly relies on identifying specific nucleotide changes—founder mutations—that have direct clinical consequences. This transition from anthropology to clinical genetics is what enables the actionable recommendations provided in the later sections of this report.

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3. The Northwest Caucasus: Circassians, Shapsugs, and Abazins

The populations of the Northwest Caucasus, encompassing the Adyghe (Circassians), Shapsugs, Abkhaz, and Abazins, share a close linguistic and genetic affinity. Despite their dispersion across the republics of Adygea, Kabardino-Balkaria, Karachay-Cherkessia, and the Black Sea coast (Shapsugia), as well as a vast diaspora, they exhibit a distinct profile of hereditary disorders driven by a shared ancestral gene pool.

3.1 Phenylketonuria (PKU): The Karachay-Circassian Anomaly

One of the most striking medical genetic findings in the region is the extraordinarily high incidence of Phenylketonuria (PKU) in the Karachay-Cherkess Republic (KChR). While PKU is a well-known metabolic disorder globally, typically affecting 1 in 10,000 to 1 in 15,000 newborns in Europe, the incidence in KChR is the highest recorded in the world, at approximately **1:850** newborns.[8]

The driver of this epidemic is a single founder mutation in the *PAH* gene: **p.Arg261*** (c.781C>T). In the Karachay population, a Turkic-speaking group that has lived in close proximity and genetic exchange with Circassians and Abazins for centuries, the carrier frequency for this lethal recessive variant is approximately **1:16**.[8] Molecular dating using haplotype analysis of extragenic short tandem repeat (STR) loci linked to the mutation estimates its origin or expansion to approximately 10 to 13 generations ago (roughly 275 ± 73 years).[8] This timeframe coincides with the consolidation of these populations in their current mountain valleys, suggesting a bottleneck event followed by rapid population growth.

While the mutation is most concentrated in the Karachay ethnic group, the centuries of intermarriage and shared geography mean that neighboring Circassian (Adyghe) and Abazin populations are also at elevated risk. The p.Arg261* variant accounts for 68.4% of all PKU alleles in Karachay patients, a dominance that mirrors the "founder effects" seen in Finland.[10] Clinically, this mandates that any newborn in the region with elevated phenylalanine levels be tested specifically for p.Arg261* immediately, rather than waiting for full gene sequencing, to expedite dietary management and prevent neurodevelopmental damage.

3.2 Cystic Fibrosis: A Non-European Spectrum

Cystic Fibrosis (CF) screening in Europe and North America typically prioritizes the ΔF508 (F508del) mutation, which accounts for ~70% of alleles in Northern Europeans. However, relying on this standard panel for Circassian or Abazin patients is fraught with diagnostic risk. The mutational spectrum in the Northwest Caucasus is highly heterogeneous and distinct.

Recent studies have characterized the *CFTR* gene mutations in these populations, revealing a

significant prevalence of **W1282X** (c.3846G>A) and **1677delTA** (c.1545_1546delTA).[11]

- **W1282X:** This severe nonsense mutation is well-known as the primary Ashkenazi Jewish CF mutation. Its presence at high frequencies in the Northwest Caucasus—particularly in Karachays (where it constitutes ~90% of CF alleles) and Abazins—is a profound genetic link that hints at either shared ancient Middle Eastern ancestry or historical gene flow.[13] In Abazins, W1282X co-exists with F508del and 1677delTA, creating a complex carrier landscape.[12]
- **1677delTA:** This mutation is another major regional founder, found in Circassians and Abazins. In neighboring Georgia, it is the most common mutation (42.7%), surpassing F508del.[14] This suggests that 1677delTA is a "Caucasus-specific" variant that predates the diversification of modern ethnic groups in the region.

The clinical implication is clear: a standard "23-mutation panel" designed for Western populations will miss a substantial proportion of CF carriers in Adygea and Karachay-Cherkessia. Genetic counseling for Circassian families must utilize panels that specifically include W1282X and 1677delTA to ensure accurate risk assessment.

3.3 Rare Disorders and Novel Variants

The high degree of endogamy in rural Circassian and Abazin communities has led to the accumulation of rare and ultra-rare hereditary conditions. The medical genetic registries of the Karachay-Cherkess Republic and Adygea provide a window into this hidden burden.

Ehlers-Danlos Syndrome and Connective Tissue Disorders:
Studies have identified a notably high prevalence of Ehlers-Danlos Syndrome (Autosomal Dominant types) in the Abazin population, with a calculated prevalence of 1:1,383—significantly higher than the global average.15 This clustering suggests a local founder effect in a dominant gene (likely COL5A1 or COL5A2), although specific molecular characterization remains an active area of research.
Genodermatoses:
Keratosis Palmoplantaris, a group of disorders characterized by thickening of the skin on the palms and soles, shows a high frequency of 1:2,371 in Abazins.15 Similarly, X-linked Ichthyosis is prevalent, with distinct molecular mechanisms identified in different ethnic isolates within the same region, reinforcing the "genetic archipelago" model of the Caucasus.3
Ophthalmological and Neurological Conditions:
The Circassian population exhibits elevated rates of Congenital Cataract (1:16,939) and Sensorineural Nonsyndromic Deafness (1:3,176), both exceeding the Russian Federation averages.16 Furthermore, a high burden of undiagnosed familial mental retardation and microcephaly (1:7,258) points to a reservoir of uncharacterized recessive neurological mutations circulating in these populations.16 A novel de novo variant in TRPV4 (c.245C>T) causing Metatropic Dysplasia was also recently characterized in a Circassian family, expanding the known phenotypic spectrum of this gene.17

3.4 G6PD Deficiency: The Forgotten Trait

While often associated with African or Mediterranean populations, **Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency** is a significant, yet historically overlooked, feature of the Circassian genetic profile. Early studies identified G6PD deficiency in Circassians, linking it to the "Caucasus" haplotype of the gene.[18]

Unlike the "African" (A-) variant, the variants found in the Caucasus (often Class II, severe deficiency) make individuals highly susceptible to hemolysis upon exposure to fava beans or oxidative drugs. Historical accounts and genetic data from the diaspora suggest that G6PD deficiency was common enough to be a noted trait, likely maintained by the historical presence of malaria in the marshy lowlands of the Kuban River basin before the drainage projects of the 19th and 20th centuries.[18] Clinicians treating patients of Circassian descent should remain vigilant for drug-induced hemolysis, a risk often not immediately associated with "Caucasian" patients in Western practice.

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4. The Central Caucasus: The Ossetian Isolate

The Ossetians occupy a unique position in the genetic landscape of the Caucasus. As speakers of an Iranian language (descended from Scythian/Sarmatian/Alanic dialects), they are linguistically distinct from their Northwest (Adyghe) and Northeast (Nakh-Dagestanian) neighbors. This distinctiveness is mirrored in their genetic architecture, which displays a unique set of founder mutations.

4.1 Hereditary Hearing Loss: The *GJB2* Spectrum

Hearing loss is one of the most common congenital disorders, and the *GJB2* gene (Connexin 26) is the most frequent culprit. However, the mutational spectrum in Ossetians differs radically from the European norm.

In most European populations, the **c.35delG** mutation is responsible for the vast majority of *GJB2*-related hearing loss. While present in Ossetians, its frequency (~38% of alleles) is significantly lower than in Russians (~83%).[20] Instead, the Ossetian population is characterized by a specific founder deletion: **c.358_360delGAG** (also known as delGAG). This mutation results in the loss of a glutamate residue and is functionally deleterious.

In a recent cohort of Ossetian patients with non-syndromic hearing loss, the homozygous **c.358_360delGAG/c.358_360delGAG** genotype was the single most common cause of deafness, accounting for ~40% of cases.[20] This finding has profound implications for screening. A genetic test designed for the "standard" European mutations might only screen for c.35delG. If an Ossetian patient is homozygous for c.358_360delGAG, such a test would return a "negative" result, leading to a missed diagnosis. Therefore, full sequencing of the

GJB2 coding exon is mandatory for any Ossetian patient presenting with hearing loss.

4.2 Cystic Fibrosis and X-Linked Disorders

The profile of Cystic Fibrosis in Ossetians further highlights their genetic distinctiveness. Ossetians carry both the **W1282X** mutation (typical of Karachays/Ashkenazim) and **F508del** (typical of Europeans), but at lower frequencies than the peak populations for these variants.[11] The presence of W1282X (allele frequency 0.0032) in Ossetians reinforces the hypothesis of a widespread, ancient "Alano-Khazar" or Near Eastern substrate that pervades the Central and North Caucasus.[12]

In the realm of X-linked disorders, recent research into **X-linked Ichthyosis** (caused by *STS* gene deletions/mutations) in North Ossetia-Alania revealed that Ossetian families carried distinct *STS* nucleotide substitutions compared to Kumyk or Turkish families living in the same republic.[3] This seemingly minor detail underscores a major demographic reality: despite sharing a small geographic administrative region, these ethnic groups have maintained high levels of reproductive isolation (endogamy) for centuries, preventing the homogenization of their rare disease pools.

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5. The Northeast Caucasus: Chechens and Ingush

The Nakh-speaking peoples (Chechens and Ingush) exhibit perhaps the strongest evidence for founder effects in the entire region. This is likely a consequence of strict clan-based social structures (*teip*) which, while exogamous internally, create a closed breeding population at the ethnic level, combined with the severe population bottlenecks of the 1944 deportation.

5.1 BRCA1: The "Chechen" Founder Mutation

One of the most clinically significant discoveries of the 2015–2025 period is the identification of a high-frequency *BRCA1* founder mutation in the Chechen population. Historically, *BRCA* testing has been guided by family history or "Ashkenazi" panels. However, a study of Chechen women with breast and ovarian cancer identified the **c.3629_3630delAG** variant as a recurrent pathogenic allele.[21]

This mutation was found to drive a "strong founder effect," accounting for a significant proportion of hereditary cancer cases in the republic. The identification of a specific high-risk allele in this population allows for the development of a targeted, cost-effective screening strategy similar to the "Ashkenazi Panel." Chechen women presenting with breast or ovarian cancer—or those with a family history—should be prioritized for testing of the **c.3629_3630delAG** variant. Early identification allows for prophylactic measures (e.g., mastectomy, oophorectomy) and targeted therapies (PARP inhibitors), potentially saving lives

in a population where cancer diagnosis is often delayed.

5.2 Cystic Fibrosis: The Dominance of 1677delTA

The genetic landscape of Cystic Fibrosis in Chechnya is starkly different from both Russia and Europe. In the Chechen population, the **1677delTA** (c.1545_1546delTA) mutation is the overwhelming driver of the disease.

Research indicates that **81.5%** of CF alleles in Chechen patients are 1677delTA.[12] This degree of homogeneity is extremely rare in large populations and is comparable to the dominance of F508del in Northern Europe. This dominance makes "Chechen CF" a distinct genetic entity. Clinically, patients homozygous for 1677delTA often present with severe pancreatic insufficiency. However, some studies suggest that while liver involvement and growth retardation are common, the respiratory phenotype might be slightly distinct from the classic F508del presentation, with lower frequencies of certain chronic complications, though severe lung disease still inevitably develops.[14] The sheer prevalence of this single mutation simplifies carrier screening: a single-variant test for 1677delTA could detect over 80% of carriers in the Chechen population.

5.3 The Ingush-Specific *GJB2* Deletion

The Ingush population, closely related to the Chechens, possesses its own unique genetic burden. A study of hereditary hearing loss in Ingushetia identified a large deletion in the *GJB2* gene: **del(GJB2-D13S175)**.[22]

This deletion encompasses the coding region of the gene and is estimated to be approximately **3,000 years old**, dating back to the Iron Age ancestors of the Nakh peoples. Crucially, standard PCR-based genetic tests designed to detect small mutations (like c.35delG) will **miss this deletion entirely**. The deletion removes the primer binding sites or the target sequence, often leading to a false "homozygous normal" or "heterozygous" readout if only one allele is deleted. Diagnosis requires techniques capable of detecting copy number variations (CNVs), such as MLPA (Multiplex Ligation-dependent Probe Amplification). The high frequency of this "invisible" mutation in the Ingush population is a critical pitfall for clinical geneticists to be aware of.

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6. Auto-Inflammatory Diseases: FMF and Behcet's

The "Silk Road" legacy of the Caucasus is most evident in the prevalence of auto-inflammatory diseases, which are shared with neighboring Anatolian and Middle Eastern populations.

6.1 Familial Mediterranean Fever (FMF)

Familial Mediterranean Fever, caused by mutations in the *MEFV* gene, is the archetype of region-specific genetic disorders. While most prevalent in Armenians, Turks, and Jews, it is also a significant health issue for North Caucasus populations, particularly in the Diaspora.

- **Circassian Diaspora:** In Jordan and Turkey, where Circassians have intermarried with local populations or lived in endogamous enclaves for 150 years, FMF carrier rates are notable. Studies in Jordan estimate FMF prevalence at around 0.04%, but carrier rates for *MEFV* mutations (M694V, V726A, E148Q) are high.[23] The **M694V** mutation, associated with a more severe phenotype and amyloidosis risk, is common in these groups.[25]
- **Homeland:** In the North Caucasus homeland, FMF is often underdiagnosed, frequently mistaken for other periodic fevers or "rheumatism." However, the genetic proximity to populations with high *MEFV* mutation loads implies a significant undiagnosed burden. Screening for the "Mediterranean" panel of *MEFV* mutations is recommended for any North Caucasian patient presenting with recurrent unexplained fevers or polyserositis.

6.2 Behcet's Disease

Behcet's Disease, a systemic vasculitis, is famously known as the "Silk Road Disease." Its distribution follows the ancient trade routes from Japan to the Mediterranean. The North Caucasus lies directly on the northern branch of this route.

- **Genetic Susceptibility:** The strongest genetic risk factor is the **HLA-B51** allele.[26] While direct prevalence studies in Adygea are scarce, the surrounding regions (Turkey, Iran, Southern Russia) have high rates.
- **Clinical Presentation:** Manifestations include oral/genital ulcers and uveitis. In the Caucasus context, identifying HLA-B51 in patients with these symptoms can support the diagnosis. The disease is thought to be triggered by environmental factors (infectious agents) acting on this susceptible genetic background, a dynamic well-suited to the varied ecology of the Caucasus.[28]

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7. Genomic Architecture: Consanguinity, ROH, and FROH

The burden of recessive disease is inextricably linked to population structure. A key finding of this report is the "Paradox of Structure" between Homeland and Diaspora populations.

7.1 The Paradox: Homeland Exogamy vs. Diaspora Endogamy

Traditional social norms in the North Caucasus (Adyghe Xabze, Chechen Adat) mandate strict **exogamy**. Individuals are forbidden from marrying within their own clan (*teip*, *tlapq*) or often even with anyone sharing a surname for 7 generations. In the homeland, this practice historically maintained genetic diversity despite small population sizes.

However, the 19th-century Diaspora upended this dynamic. Circassian and Chechen

communities in Jordan, Turkey, and Syria found themselves as ethnic minorities. To preserve their culture and language, they shifted toward strict **ethnic endogamy** (marrying only other Circassians) and, in some cases, adopted the local Arab/Middle Eastern custom of **consanguinity** (cousin marriage).

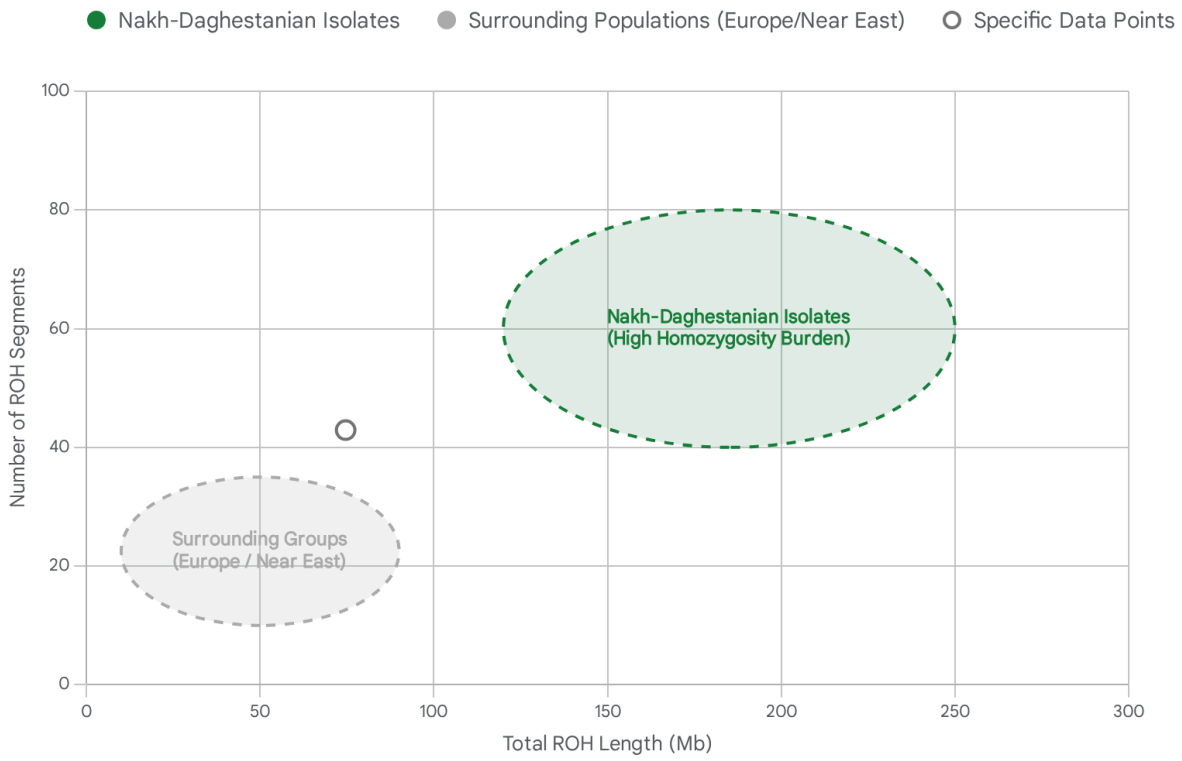
- **Jordan:** Consanguinity rates in North Jordan (a hub for Circassians) have historically reached **50-60%.**[29]
- **Consequence:** This shift has created two distinct genetic profiles for the "same" ethnic group. A Circassian from Maikop (Homeland) may have a genome characterized by "ancient isolation" (short Runs of Homozygosity), while a Circassian from Amman (Diaspora) may show "recent inbreeding" (long Runs of Homozygosity), significantly increasing the risk of recessive diseases like FMF or rare metabolic disorders.[31]

7.2 Runs of Homozygosity (ROH) and Inbreeding Coefficients (F_{ROH})

Genomic analysis of North Caucasian populations reveals a high burden of **Runs of Homozygosity (ROH)**—long stretches of the genome where both maternal and paternal copies are identical.

- **Dagestan Isolates:** Studies of Nakh-Dagestanian speakers have recorded "very high numbers and long lengths of ROH" and elevated genomic inbreeding coefficients (F_{ROH}) compared to cosmopolitan European groups.[32] This indicates that despite exogamy rules, the effective population size in isolated mountain auls was small enough to cause cryptic inbreeding.
- **Clinical Impact:** High F_{ROH} correlates with the "homozygosity burden," increasing the expression of deleterious recessive mutations. This explains the high load of rare disorders (e.g., mental retardation, deafness) observed in rural districts of KChR and Dagestan.[33]

Genomic Homozygosity Burden: North Caucasus vs. Global Populations



ROH distribution. Dagestan and North Caucasus isolates (Green/Blue) cluster in the upper right (high burden), indicating both ancient isolation and reduced effective population size. Contrast with Outbred Europeans (Gray) in the lower left.

Data sources: PubMed (Nakh-Daghestanian Study), UCL Thesis, PMC Study, bioRxiv

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8. Comparative Genetics: The Caucasus vs. Ashkenazi and Finnish Models

The genetic structure of the North Caucasus bears a striking resemblance to well-studied founder populations like Ashkenazi Jews (AJ) and Finns. Understanding these parallels is key to designing effective public health strategies.

8.1 The Ashkenazi Parallel

Both the Ashkenazi Jewish and North Caucasus populations (specifically Chechens and

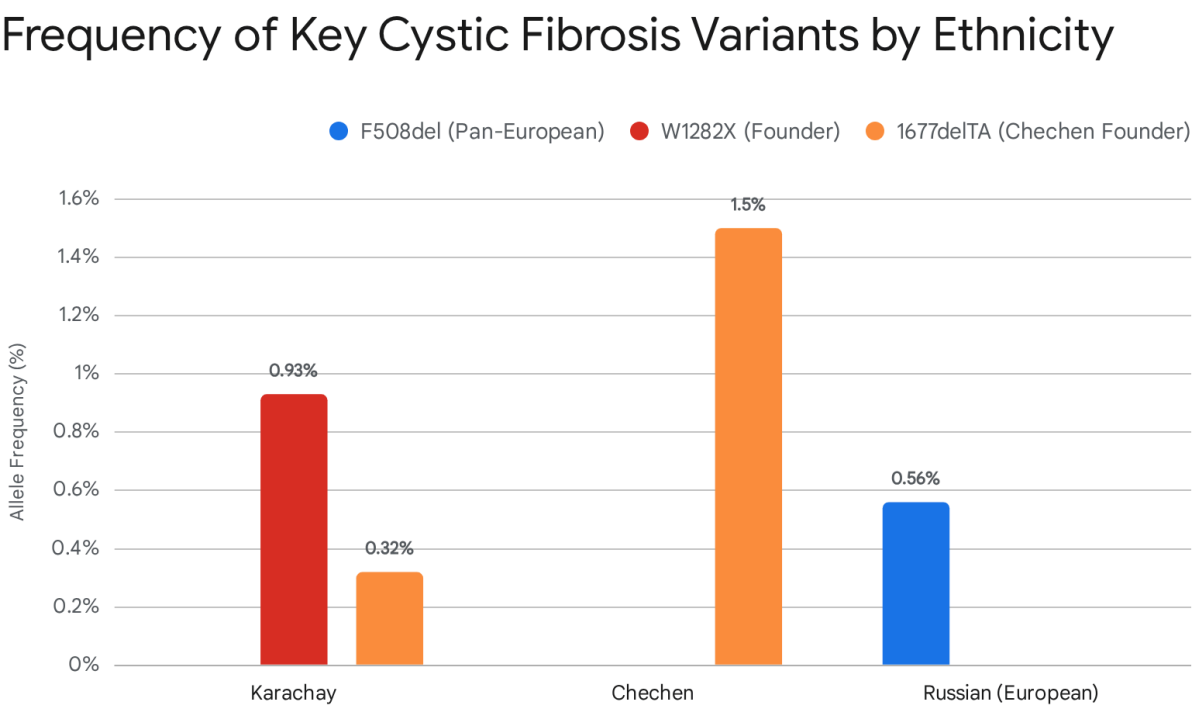
Karachays) share a specific demographic history: a small founding group, followed by rapid expansion, maintained by endogamy. This has led to the elevation of specific lethal recessive mutations to high frequencies.

- **Shared Mutations:** The most notable link is the **W1282X** mutation in *CFTR*. It is a principal founder mutation in both Ashkenazi Jews and Karachays/Ossetians. This shared burden suggests a deep genetic connection, potentially linked to the Khazar Khaganate or shared movements from the Near East during the Diaspora.[13]
- **Parallel Burdens:**
  - **AJ:** Tay-Sachs, Canavan, BRCA1 (185delAG).
  - **Chechen:** BRCA1 (c.3629_3630delAG), CF (1677delTA).
  - **Karachay:** PKU (p.Arg261*), CF (W1282X).
- **Strategic Lesson:** The AJ community has benefited immensely from the "Dor Yeshorim" and "panel testing" models. The data suggests that Chechens and Karachays would benefit from similar "ethnic panels" that prioritize their specific founder mutations over generic sequencing.

8.2 The Finnish Disease Heritage (FDH) Model

The Finnish population is famous for the "Finnish Disease Heritage"—a set of rare diseases common in Finland but rare elsewhere. The Caucasus mirrors this with its own set of "private" diseases (e.g., the specific *GJB2* deletion in Ingush, the high rate of Metatropic Dysplasia in Circassians).

- **Lesson:** Just as "Finnish variant" is a standard annotation in genomic databases, "Caucasian variants" must be curated. Currently, many of these variants might be classified as Variants of Uncertain Significance (VUS) in Western clinics because they are absent from control databases like gnomAD (which lacks substantial North Caucasian representation).



Comparison of allele frequencies for major CFTR variants. Note the dominance of W1282X in Karachays and 1677delTA in Chechens, contrasting with the standard European F508del profile.

Data sources: Frontiers in Genetics (2021), PubMed (2016), PMC (2021), PubMed (2021)

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9. Hemoglobinopathies: A Regional Overview

While Hemoglobinopathies (Thalassemia, Sickle Cell) are often framed as "Mediterranean" or "African" issues, the North Caucasus and Transcaucasus are significant foci for these disorders, driven by the historical prevalence of malaria in the warm, marshy lowlands of the region.

9.1 Beta-Thalassemia in the Caucasus

Beta-Thalassemia is the most significant hemoglobinopathy in the region.

- **Adygea and Krasnodar Krai:** Historical data identifies this region as a "focus" of beta-thalassemia in the Russian Federation.[34] The prevalence is driven by the historical endemicity of malaria in the Kuban river delta. While modern data for Adygea specifically is less dense than for Dagestan, the proximity suggests a similar risk profile.
- **Dagestan:** Identified as the "most endemic region" for hemoglobinopathies in Russia. Recent studies (2020) characterized the spectrum, finding a diverse array of *HBB*

mutations, including classic Mediterranean variants (IVS-I-110) and rarer forms.[35]

- **Azerbaijan (Neighboring Context):** As a genetic proxy for the South Caucasus influence, Azerbaijan has a very high carrier rate (4-8.6%). The spectrum is dominated by Codon 8 (-AA) and IVS-II-1 (G>A).[36] This high prevalence suggests that gene flow from the south likely introduced these variants into North Caucasus populations like the Ossetians and Dagestanis.

9.2 Sickle Cell Disease (SCD)

Sickle Cell Disease is less prevalent than Thalassemia but is emerging as a concern due to global migration and admixture. The *HbS* allele is found in the Caucasus but typically at lower frequencies than in the Middle East or Africa. However, the presence of **Sickle-Beta Thalassemia** (a compound heterozygous condition) is a real risk in populations where both traits circulate, such as in the diverse ethnic mix of Dagestan and the cosmopolitan areas of Krasnodar.[37]

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10. Public Health Strategy and Screening Recommendations

The distinct genetic architecture described in this report necessitates a revision of current screening guidelines for patients of North Caucasian ancestry. We propose a tiered, ethnicity-specific screening algorithm.

10.1 Tiered Screening Panels (The "Caucasus Panels")

Clinicians should move beyond "pan-ethnic" screens and utilize these targeted lists as the first line of investigation or to supplement negative WES results.

Table 1: Proposed Ethnic-Specific Mutation Panels

Panel Target	Primary Gene	Key Mutations (Legacy/HGVS)	Target Population	Clinical Rationale
Circassian / Karachay	*PAH*	p.Arg261* (c.781C>T)	Karachay, Circassian, Abazin	Highly prevalent (1:16 carriers in Karachay). Major cause of PKU.

	CFTR	W1282X, 1677delTA	Karachay, Circassian	W1282X is ~90% of Karachay CF alleles.
	G6PD	"Caucasus" Variants	Circassian (Shapsug)	Risk of drug-induced hemolysis.
Chechen / Ingush	*BRCA1*	**c.3629_3630delAG**	Chechen	Strong founder effect in breast/ovarian cancer. High priority for women >30.
	CFTR	**1677delTA**	Chechen	Accounts for ~81% of CF alleles.
	GJB2	**del(GJB2-D13S175)**	Ingush	**Invisible to standard PCR**. Requires MLPA.
Ossetian	*GJB2*	**c.358_360delGAG**	Ossetian	Main cause of hearing loss (~40%). Missed by c.35delG tests.
	STS	Deletion/Point Mutations	Ossetian	Cause of X-linked Ichthyosis.

10.2 Premarital and Carrier Screening Implementation

- **Diaspora (Jordan/Turkey):** Jordan currently mandates premarital screening for Thalassemia. Given the high receptivity of the young Jordanian population to genetic testing [39] and the high rates of consanguinity, there is a strong case for expanding the

mandatory panel for Circassian and Chechen sub-populations to include their specific founder mutations (e.g., FMF *MEFV* panel, Chechen *BRCA1*, Karachay *PAH*). This would be a high-yield public health intervention.
- **Homeland (Russia):** The focus should be on **Newborn Screening (NBS)** follow-up. In Karachay-Cherkessia, a positive NBS for phenylketonuria should trigger an immediate reflex test for the p.Arg261* mutation. This confirms the genetic diagnosis rapidly and allows for precise family counseling regarding future pregnancies.

10.3 Guidelines for Genetic Counselors

1. **Nuance in Ancestry:** Counselors must distinguish between "Russian citizenship" and "Caucasian ethnicity." A patient from Russia may be ethnically Chechen, Ossetian, or Russian, each requiring a completely different testing strategy.
2. **The "Hidden" Deletions:** Be explicitly aware of the Ingush *GJB2* deletion. If an Ingush child has hearing loss and a "normal" sequence, the counselor *must* order deletion/duplication testing (MLPA).
3. **Consanguinity Sensitivity:** In Diaspora populations, counsel with sensitivity regarding cousin marriage risks, utilizing the specific carrier rates for FMF and metabolic disorders to give concrete recurrence risks rather than general estimates.

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11. Conclusion

The populations of the North Caucasus are not merely a footnote in European genetics; they represent a distinct and complex genomic reservoir. The isolation of the mountains, combined with the tumult of history—from the Bronze Age divergence to the 19th-century Diaspora—has sculpted a medical genetic landscape characterized by potent founder effects.

The data from 2015–2025 is unequivocal: the mutations driving disease in Chechnya, Ossetia, and Circassia are different from those in Moscow, Berlin, or New York. The dominance of *BRCA1* c.3629_3630delAG in Chechens, *PAH* p.Arg261* in Karachays, and *GJB2* c.358_360delGAG in Ossetians mandates a shift towards precision medicine. By recognizing these unique molecular signatures and implementing the targeted screening recommendations outlined in this report, the medical community can bridge the gap between genomic discovery and patient care for these historically underserved populations.

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