P675 Interrogating the Source: An Investigation of the Impact of Founder Variants on Residual Risk in Carrier Screening

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Background

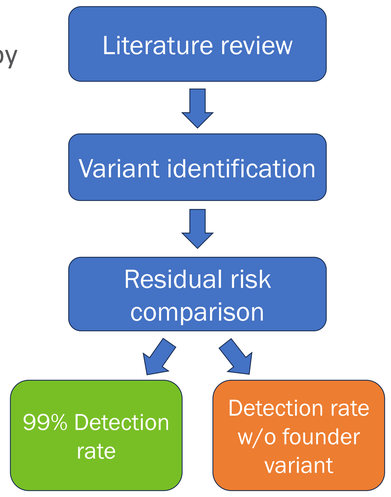
- Residual risk depends on the ability of a screening test to detect variants that are disease causing.
- Common or founder pathogenic variants play a significant role in carrier screening and residual risk reporting.
- Specific founder variants that are technically challenging may escape detection if not carefully evaluated.
- Patient-specific factors, such as family history and genetic ancestry, can impact residual risk.

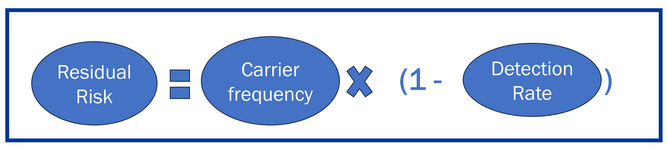
OBJECTIVE

- To demonstrate the impact founder variants have on residual risk in carrier screening.

Method

1. Reviewed the **clinical literature** for founder variants in Tier 3 genes recommended by ACMG.
2. Identified the etiologic fraction of disease attributed to the identified variants.
3. Compared residual risks of a negative carrier screening using a **theoretical test** with a 99% analytical detection rate and a **theoretical test** with a detection rate that did not include the founder variant. Residual risk was calculated using the formula below.





Conclusions

- It is important to understand the detection rate quoted on a carrier screening test.
- Residual risk will vary based on the detection rate of an assay.
- Laboratories should be aware of potential founder variants that may influence the detection rate of a carrier screen and incorporate those as appropriate.
- Providers should always take a detailed family history to determine the appropriate screening test to offer patients.

References:

Gregg, et al., (2021). Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in medicine : official journal of the American College of Medical Genetics*, *23*(10), 1793–1806. https://doi.org/10.1038/s41436-021-01203-z

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Results

Table 1: Variants That Should Be Detectable With A Standard ROI*

Disease	Gene	Variant of interest	Ethnicity of the variant	Worldwide carrier rate (1/X)**	Residual risk to be a carrier after negative test, 99% DR (1/X)	Clinical DR without the variant	Residual risk to be a carrier, no detection of founder (1/X)***	PMID Reference
Xeroderma pigmentosa	*XPC*	c.1643_1644delTG(V548Afs*25)	North Africa	20	1965	13%	**23**	20054342
Oculocutaneous albinism type 1A and 1B	*TYR*	c.929dupC(R311Kfs*7)	Chinese	20	2027	80%	**102**	34838614
Tay–Sachs disease	*HEXA*	c.749G>T(G250V)	Iraqi Jewish	30	3017	61%	**78**	14648242
Smith–Lemli–Opitz syndrome	*DHCR7*	c.278C>T(T93M)	Mediterranean Sea basin	42	4218	47%	**80**	14981719
Wilson's Disease	*ATP7B*	c.2333G>T(R778L)	East Asia	45	4549	56%	**103**	20465995
Finnish congenital nephrotic syndrome	*NPHS1*	c.1481delC(S494Cfs*55)	Old Order Mennonite	63	6252	1%	**63**	10577936
Glycogen storage disease type IA	*G6PC1*	c.379_380dupTA(Y128Tfs*3)	Hispanic	75	7462	50%	**149**	10094563
Hereditary fructosuria	*ALDOB*	c.324+1G>A	Northern India	83	8252	28%	**115**	25595217
Fanconi anemia, complementation group C	*FANCC*	c.67delG(D23Ifs*23)	Dutch	83	8339	14%	**97**	22701786
Spinocerebellar ataxia 10	*ANO10*	c.1150_1151delTT(L384Nfs*91)	Romani	93	9276	0%	**93**	22008874
Niemann–Pick disease	*SMPD1*	c.96G>A p.W32*	Italian	97	9748	81%	**520**	15241805
Mucolipidosis	*GNPTAB*	c.3503_3504delTC(L1168Qfs*5)	French Canadian	118	11834	0%	**118**	18190596
Very long chain acyl-CoA dehydrogenase deficiency	*ACADVL*	c.65>A(S22*)	Saudi Arabia	156	15579	16%	**186**	28980192
argininosuccinic aciduria	*ASL*	c.1153C>T(R385C)	Finnish	162	16155	40%	**269**	18616627
Mucopolysaccharidosis	*IDUA*	c.266G>A(R89Q)	Japanese	214	21390	76%	**891**	8664897

Table 1: Founder variants described in the literature for 15 genes recommended for carrier screening by ACMG. Ethnicity of the variant is as described in the referenced publication. * Standard ROI defined as +/- 20 bp into the intron ** Worldwide carrier frequency is from Gregg et al., 2021. *** Residual risk is specific to the ethnicity of founder variant.
DR: detection rate; ROI: region of interest.

A closer look...

A patient with Mennonite ancestry has carrier screening. → The carrier screen quotes "99% analytical detection rate," but cannot detect the c.1481delC(S494Cfs*55) variant. → The patient tests negative for any *NPHS1* variants. → ASSUMPTION: The residual risk for the patient to be a carrier is 1/6252 / REALITY: The patient's post-test risk to be a carrier (1/63) is the same as the pre-test risk

Summary: This example demonstrates the impact founder variants and detection rate have on residual risk. While this is an unlikely scenario given that the founder variant c.1481delC(S494Cfs*55) should be easily detectable, it illustrates the importance of founder variants, taking a detailed family history, and understanding the detection rate of a test when ordering carrier screening.

Table 2: Variants That Are Not Detectable With A Standard ROI*

Disease	Gene	Variant of interest	Ethnicity of the variant	Worldwide carrier rate (1/X)**	Residual risk to be a carrier after negative test, 99% DR (1/X)	Clinical DR without the variant	Residual risk to be a carrier, no detection of founder (1/X)***	PMID Reference
Hexosaminidase A deficiency	*HEXA*	c.-207-2357_253+5128delinsG (7.6-kb del)	French Canadian	30	**3017**	**20%**	**38**	32302469
Wilson disease	*ATP7B*	c.-436_-422del15	Sardinia	45	**4549**	**40%**	**75**	10502776
Hermansky Pudlak syndrome	*HPS3*	3.9-kb del	Puerto Rican	59	**5900**	**0%**	**59**	16417222
GBE1-related disorders	*GBE1*	c.2053-3358_2053-3350delGTGTGGTGGins19	Ashkenazi Jewish	72	**7247**	**77%**	**317**	25665141
Oculocutaneous albinism	*OCA2*	Exon 7 del	African	76	**7626**	**79%**	**370**	29345414
Oculocutaneous albinism	*OCA2*	LINE-mediated 122.5-kilobase deletion	Navajo	76	**7626**	**0%**	**76**	12469324
Fabry disease	*GLA*	c.640-801G>A	Taiwanese	101	**10050**	**31%**	**146**	25762495
AR polycystic kidney disease	*PKHD1*	c.7350+653A>G	French	168	**16779**	**96%**	**4661**	19021639

Table 2: Founder variants described in the literature for 7 genes recommended for carrier screening by ACMG. Ethnicity of the variant is as described in the referenced publication. * Standard ROI defined as +/- 20 bp into the intron ** Worldwide carrier frequency is from Gregg et al., 2021. *** Residual risk is specific to the ethnicity of founder variant.
DR: detection rate; ROI: region of interest.

A closer look...

A patient with Sardinian ancestry has carrier screening. → The carrier screen quotes "99% analytical detection rate," but cannot detect the c.-436_-422del15 variant. → The patient tests negative for any *ATP7B* variants. → ASSUMPTION: The residual risk for the patient to be a carrier is 1/4549 / REALITY: The patient's post-test risk to be a carrier (1/75) is only slightly reduced from the pre-test risk

Summary: This example is very similar to the first, but given that the founder variant c.-436_-422del15 is well outside a typical assay design, it is more likely to be undetected during carrier screening. This again illustrates the importance of taking a detailed family history and understanding the detection rate of a test when ordering carrier screening.