

American Journal of Human Genetics, Volume 92

Supplemental Information

**Age-Dependent Germline Mosaicism
of the Most Common Noonan Syndrome Mutation
Shows the Signature of Germline Selection**

**Song-Ro Yoon, Soo-Kung Choi, Jordan Eboreime, Bruce D. Gelb, Peter Calabrese,
and Norman Arnheim**

Supplemental Inventory

Table S1 (see separate Excel file)

Table S2

Table S3

Table S4

Table S1. Mutation Frequencies and Number of Genomes in All Testis Pieces
See Excel spreadsheet.

Table S2. Asymmetric and Symmetric Hot Spot Model Results for All Testes

Testis	Age	Model parameter Mutation rate per cell division	Mx/Av			F<50 (%)		
			Data	Simulated 95% range	p-value	Data	Simulated 95% range	p-value
Asymmetric hot spot model								
59056	19	5.7×10^{-9}	39	2 – 14	$<10^{-6}$	100	100 – 100	0.50
63878	21	4.6×10^{-8}	8	1 – 11	0.06	99	99 – 100	0.79
63205	21	1.1×10^{-9}	40	3 – 15	9×10^{-6}	100	100 – 100	0.50
60832	23	2.5×10^{-9}	20	2 – 11	0.003	100	100 – 100	0.50
62923	36	3.1×10^{-7}	130	1 – 9	$<10^{-6}$	90	0 – 0	$<10^{-6}$
59089	45	2.9×10^{-8}	31	1 – 9	$<10^{-6}$	93	99 – 100	1.00
854-2	54	1.4×10^{-6}	156	1 – 5	$<10^{-6}$	77	0 – 0	$<10^{-6}$
374-1	62	2.2×10^{-7}	129	1 – 7	$<10^{-6}$	90	0 – 0	$<10^{-6}$
374-2	62	5.3×10^{-8}	62	1 – 7	$<10^{-6}$	94	0 – 1	$<10^{-6}$
60891	68	4.2×10^{-9}	14	1 – 5	2×10^{-5}	95	100 – 100	1.00
64302	75	3.9×10^{-8}	17	1 – 7	$<10^{-6}$	90	1 – 4	$<10^{-6}$
60954	76	7.3×10^{-8}	18	1 – 7	$<10^{-6}$	81	0 – 0	$<10^{-6}$
60955	76	2.3×10^{-10}	124	3 – 5	$<10^{-6}$	100	100 – 100	0.5
57650	80	3.2×10^{-8}	7	1 – 5	0.02	76	40 – 54	$<10^{-6}$
60507	80	9.1×10^{-9}	8	1 – 4	0.005	97	99 – 100	1.00
Symmetric hot spot model								
59056	19	5.7×10^{-9}	39	13 – 42	0.10	100	100 – 100	0.50
63878	21	4.6×10^{-8}	8	4 – 15	0.11	99	98 – 100	0.39
63205	21	1.1×10^{-9}	40	30 – 114	0.84	100	100 – 100	0.50
60832	23	2.5×10^{-9}	20	20 – 70	0.97	100	100 – 100	0.50
62923	36	3.1×10^{-7}	130	2 – 9	$<10^{-6}$	90	0 – 2	$<10^{-6}$
59089	45	2.9×10^{-8}	31	5 – 13	8×10^{-4}	93	84 – 90	1×10^{-4}
854-2	54	1.4×10^{-6}	156	1 – 5	$<10^{-6}$	77	0 – 0	$<10^{-6}$
374-1	62	2.2×10^{-7}	129	2 – 6	$<10^{-6}$	90	0 – 1	$<10^{-6}$
374-2	62	5.3×10^{-8}	62	4 – 9	$<10^{-6}$	94	47 – 58	$<10^{-6}$
60891	68	4.2×10^{-9}	14	14 – 47	0.98	95	96 – 98	1.00
64302	75	3.9×10^{-8}	17	4 – 10	0.004	90	53 – 64	$<10^{-6}$
60954	76	7.3×10^{-8}	18	3 – 8	0.002	81	21 – 31	$<10^{-6}$
60955	76	2.3×10^{-10}	124	57 – 188	0.43	100	99 – 100	0.77
57650	80	3.2×10^{-8}	7	5 – 11	0.31	76	59 – 69	8×10^{-6}
60507	80	9.1×10^{-9}	8	9 – 27	0.99	97	89 – 94	4×10^{-6}

Table S3. Asymmetric and Symmetric Selection Model Results for All Testes

Testis	Age	Model parameters		Mx/Av			F<50 (%)		
		Mutation rate per cell division	Selection parameter	Data	Simulated 95% range	p-value	Data	Simulated 95% range	p-value
Asymmetric selection model									
59056	19	5.6×10^{-10}	0.026	39	13 – 52	0.08	100	100 – 100	0.50
63878	21	4.2×10^{-9}	0.020	8	4 – 13	0.13	99	99 – 100	0.52
63205	21	1.8×10^{-10}	0.016	40	19 – 68	0.27	100	100 – 100	0.50
60832	23	2.7×10^{-10}	0.016	20	15 – 50	0.77	100	100 – 100	0.50
62923	36	3.7×10^{-11}	0.022	130	37 – 157	0.09	90	90 – 97	0.96
59089	45	9.6×10^{-11}	0.011	31	20 – 72	0.64	93	88 – 94	0.10
854-2	54	1.3×10^{-11}	0.015	156	39 – 171	0.06	77	89 – 97	1.00
374-1	62	1.6×10^{-11}	0.011	129	39 – 164	0.12	90	90 – 97	0.97
374-2	62	2.6×10^{-11}	0.0095	62	33 – 135	0.56	94	90 – 96	0.33
60891	68	2.3×10^{-10}	0.0051	14	8 – 26	0.39	95	98 – 100	1.00
64302	75	1.2×10^{-10}	0.010	17	17 – 59	0.97	90	80 – 88	0.003
60954	76	1.2×10^{-10}	0.0105	18	0 – 61	0.96	81	76 – 85	0.38
60955	76	1.1×10^{-11}	0.0079	124	50 – 178	0.28	100	100 – 100	0.50
57650	80	6.1×10^{-10}	0.0095	7	7 – 24	0.94	76	65 – 75	0.01
60507	80	9.6×10^{-10}	0.0083	8	5 – 19	0.40	97	93 – 97	0.02
Symmetric selection model									
59056	19	4.3×10^{-9}	0.0022	39	15 – 50	0.10	100	100 – 100	0.50
63878	21	3.3×10^{-8}	0.0016	8	5 – 19	0.33	99	98 – 100	0.12
63205	21	1.4×10^{-9}	0.0004	40	27 – 100	0.72	100	100 – 100	0.50
60832	23	2.2×10^{-9}	0.0008	20	21 – 75	0.98	100	100 – 100	0.50
62923	36	5.9×10^{-10}	0.0078	130	34 – 140	0.04	90	88 – 96	0.86
59089	45	3.4×10^{-9}	0.0024	31	16 – 55	0.34	93	86 – 92	0.01
854-2	54	9.2×10^{-11}	0.0064	156	46 – 190	0.15	77	92 – 99	1.00
374-1	62	4.0×10^{-10}	0.0038	129	38 – 160	0.11	90	90 – 97	0.96
374-2	62	7.9×10^{-10}	0.0028	62	32 – 127	0.49	94	89 – 96	0.23
60891	68	7.7×10^{-9}	0.0007	14	11 – 34	0.80	95	96 – 99	0.99
64302	75	6.0×10^{-9}	0.0034	17	12 – 39	0.66	90	83 – 92	0.18
60954	76	3.5×10^{-9}	0.0040	18	16 – 54	0.92	81	73 – 83	0.12
60955	76	2.0×10^{-10}	0.0030	124	63 – 192	0.54	100	99 – 100	0.67
57650	80	6.3×10^{-9}	0.0039	7	12 – 40	1.00	76	74 – 83	0.67
60507	80	2.1×10^{-8}	0.0030	8	7 – 20	0.77	97	90 – 98	0.13

Table S4. General Hot Spot Model to Examine the Symmetric Division Scheme

Model parameter q	Simulated 95% range	
	Mx/Av	F<50 (%)
0.00 (asymmetric model)	1 – 7	0 – 1
0.10	2 – 7	37 – 48
0.20	3 – 8	43 – 54
0.30	3 – 8	46 – 57
0.40	4 – 9	47 – 58
0.50 (symmetric model)	4 – 9	47 – 58

In the general hot spot model there are three possibilities: SrAp divide symmetrically to produce two SrAp with probability q, SrAp differentiate thus ending that particular SrAp lineage with probability q (the first two possibilities have to be balanced to keep the number of SrAp approximately constant), and SrAp divide asymmetrically with probability 1-2q. Simulations were made for testis 374-2 with the mutation rate per cell division equal to 5.3×10^{-8} (as in Table 2). Mutation clustering increases with the value of parameter q, but even for the greatest possible value (q = 0.5, symmetric model) the clustering is significantly less than in the testis (Mx/Av = 62, F<50 = 94%).