Supplementary Online Content

Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of *CDH1* penetrance estimates in clinically ascertained families vs families ascertained for multiple gastric cancers. *JAMA Oncol*. Published online June 27, 2019. doi:10.1001/jamaoncol.2019.1208

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Previously Published Penetrance Estimates

	Hansford 2015 % (95% CI)		Kaurah 2007 % (95% CI)		Pharoah 2001 % (95% CI)	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Gastric	70% (59-80)	56% (44-69)	40% (12-91)	63% (19-99)	67% (39-99)	83% (58-99)
Breast	--	42% (23-68)	--	52% (29-94)	--	39% (12-84)
Ascertainment	N = 75 Families 17* from this study & 58 from the literature Inclusion Criteria: 2010 IGCLC criteria.* Sample with a mean of 4 and a median of 3 gastric cancers per family.		N = 4 Families (All four families had CDH1 c.2398delC) Inclusion Criteria: Clinical diagnosis of HDGC based on previously established clinical criteria.^ All 4 families were reported to have ≥3 gastric cancers.		N = 11 Families Inclusion Criteria: At least 3 cases of diffuse gastric cancer, and at least 1 affected family member who tested positive for a CDH1 pathogenic variant.	

*Fitzgerald 2010
^Brooks-Wilson 2004 and Suriano 2005

eTable 2. Unique Germline *CDH1* Pathogenic Variants Identified

Domain	Gene	Variant	Variant Type
Protein Signal	CDH1	c.48+1G>A	Canonical Splice
Precursor Sequence	CDH1	c.202delT (p.Tyr68IlefsX15)	Frameshift
	CDH1	c.208dupT (p.Ser70PhefsX24)	Frameshift
	CDH1	c.220C>T (p.Arg74Ter)	Nonsense
	CDH1	c.315delC (p.Thr106ProfsX11)	Frameshift
	CDH1	c.337A>T (p.Lys113Ter)	Nonsense
	CDH1	c.455_465del11 (p.Gln152LeufsX12)	Frameshift
Cadherin 1	CDH1	c.467G>A (p.Trp156Ter)	Nonsense
	CDH1	c.468G>A (p.Trp156Ter)	Nonsense
	CDH1	c.489C>A (p.Cys163Ter)	Nonsense
	CDH1	c.521dupA (p.Asn174LysfsX25)	Frameshift
	CDH1	c.687+1G>C	Canonical Splice
	CDH1	c.707C>A (p.Ser236Ter)	Nonsense
Cadherin 2	CDH1	c.833-2A>G	Canonical Splice
	CDH1	c.1003C>T (p.Arg335Ter)	Nonsense
	CDH1	c.1031_1032dupTG (p.Val345TrpfsX12)	Frameshift
Cadherin 3	CDH1	c.1137+1G>A	Canonical Splice
	CDH1	c.1137G>A (p.Thr379=)	Cryptic Splice
	CDH1	c.1312delA (p.Thr438GlnfsX17)	Frameshift
	CDH1	c.1320+1G>A	Canonical Splice
	CDH1	c.1320+1G>C	Canonical Splice
	CDH1	c.1354_1357delCTAC (p.Leu452ThrfsX2)	Frameshift
Cadherin 4	CDH1	c.1476_1477delAG (p.Arg492SerfsX44)	Frameshift
	CDH1	c.1553_1565+39del52	Intronic/Exonic Deletion
	CDH1	c.1565+1delG	Canonical Splice
	CDH1	c.1565+1G>A	Canonical Splice
	CDH1	c.1565+2_1565+3insTT	Canonical Splice
	CDH1	c.1578G>A (p.Trp526Ter)	Nonsense
	CDH1	c.1587dupT (p.Ala530CysfsX7)	Frameshift
	CDH1	c.1590dupC (p.Asn531GlnfsX6)	Frameshift
	CDH1	c.1679C>G (p.Thr560Arg)	Cryptic Splice
	CDH1	c.1711+1G>C	Canonical Splice
	CDH1	c.1733dupC (p.Gly579ArgfsX9)	Frameshift
	CDH1	c.1746dupG (p.Leu583AlafsX5)	Frameshift
	CDH1	c.1779dupC (p.Ile594HisfsX11)	Frameshift

Cadherin 5	CDH1	c.1792C>T (p.Arg598Ter)	Nonsense
	CDH1	c.1979dupT (p.Asp662Ter)	Nonsense
	CDH1	c.1999delC (p.Leu667SerfsX12)	Frameshift
	CDH1	c.2064_2065delTG (p.Cys688Ter)	Nonsense
Transmembrane	CDH1	c.2164+2T>C	Canonical Splice
Cytoplasmic	CDH1	c.2195G>A (p.Arg732Gln)	Cryptic Splice
	CDH1	c.2276delG (p.Gly759GlufsX11)	Frameshift
	CDH1	c.2287G>T (p.Glu763Ter)	Nonsense
	CDH1	c.2398delC (p.Arg800AlafsX16)*^	Frameshift
	CDH1	c.2430delT (p.Phe810LeufsX6)*	Frameshift
	CDH1	c.2446A>T (p.Lys816Ter)*	Nonsense
	CDH1	Deletion Exons 1-2	Large Deletion
	CDH1	Deletion Exon 3	Large Deletion
	CDH1	Duplication Exon 3	Large Duplication
	CDH1	Deletion Exons 4-6	Large Deletion
	CDH1	Deletion Exons 7-8	Large Deletion
	CDH1	Deletion Exon 16 with Extension into the 3' UTR	Large Deletion

*NMD=No; upstream of most 3' truncating variant (c.2506G>T, p.Glu836Ter) published (Krempely 2018)
^Newfoundland founder variant (Kaurah 2007)

eTable 3. Gastric Cancer Observed by Age in Men From 41 Pedigrees With Expected Cancers by Age Based on SEER Data and Estimated Cumulative Risk Presented for Comparison.

MALE gastric cancer																			
	Probability of CDH1 from pedigree*															Cumulative risk			
Age range for pedigree counts	1			0.5			0.25			0.25>x>0			0			Age	SEER	CDH1	95% CI
	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer				
<25	13	0	0	42	0	0	27	1	0	22	0	0	23	0	0	25	0	0.0005	(0.0003,0.0007)
26-35	4	0	0.00004	12	0	0.00012	13	0	0.00013	11	0	0.00011	12	0	0.00012	30	0.00001	0.0018	(0.0012,0.0027)
36-45	9	1	0.00018	11	3	0.00022	17	3	0.00034	16	1	0.00032	16	0	0.00032	40	0.00002	0.0095	(0.0061,0.0142)
46-55	11	1	0.00077	17	4	0.00119	23	1	0.00161	29	1	0.00203	7	0	0.00049	50	0.00007	0.0347	(0.0224,0.0516)
56-65	12	2	0.00204	24	2	0.00408	30	5	0.0051	9	1	0.00153	10	0	0.0017	60	0.00017	0.0987	(0.0646,0.1447)
66-75	5	0	0.0018	21	1	0.00756	32	2	0.01152	16	2	0.00576	22	0	0.00792	70	0.00036	0.2270	(0.1523,0.3214)
76+	3	1	0.00183	18	1	0.01098	19	0	0.01159	2	0	0.00122	8	0	0.00488	80	0.00061	0.4210	(0.2952,0.5616)

* Probability of having a pathogenic CDH1 variant is calculated using relationship to known carriers for ungenotyped individuals

eTable 4. Gastric Cancers Observed by Age in Women From 41 Pedigrees With Expected Cancers by Age Based on SEER Data and Estimated Cumulative Risk Presented for Comparison.

FEMALE gastric cancer																			
	Probability of CDH1 from pedigree*															Cumulative risk			
Age range for pedigree counts	1			0.5			0.25			0.25>x>0			0			Age	SEER	CDH1	CDH1 95% CI
	n	with cancer	SEER expected cancer	n	cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer				
<25	9	0	0	39	2	0	26	2	0	20	0	0	19	0	0	25	0	0.0010	(0.0006,0.0014)
26-35	14	1	0.00014	6	2	0.00006	17	0	0.00017	21	1	0.00021	19	0	0.00019	30	0.00001	0.0027	(0.0016,0.0038)
36-45	15	2	0.0003	11	1	0.00022	12	0	0.00024	18	1	0.00036	26	0	0.00052	40	0.00002	0.0142	(0.0087,0.0200)
46-55	14	2	0.0007	13	3	0.00065	31	0	0.00155	30	1	0.0015	13	0	0.00065	50	0.00005	0.0410	(0.0252,0.0575)
56-65	21	2	0.00168	21	0	0.00168	40	0	0.0032	11	0	0.00088	12	0	0.00096	60	0.00008	0.0923	(0.0574,0.1280)
66-75	5	1	0.00085	16	2	0.00272	37	1	0.00629	11	0	0.00187	20	0	0.0034	70	0.00017	0.1810	(0.1147,0.2463)
76+	6	0	0.0018	13	0	0.0039	28	0	0.0084	2	0	0.0006	13	0	0.0039	80	0.0003	0.3275	(0.2147,0.4303)

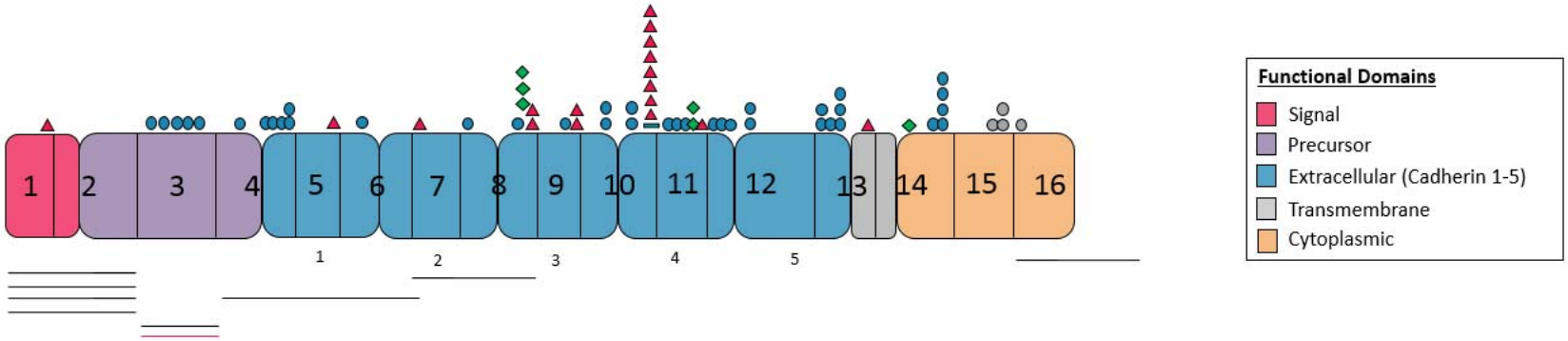
* Probability of having a pathogenic CDH1 variant is calculated using relationship to known carriers for ungenotyped individuals

eTable 5. Breast Cancer Observed by Age in Women From 41 Pedigrees With Expected Cancers by Age Based on SEER Data and Estimated Cumulative Risk Presented for Comparison.

FEMALE breast cancer																			
	Probability of CDH1 from pedigree *															Cumulative risk			
Age range for pedigree counts	1			0.5			0.25			0.25>x>0			0			Age	SEER	CDH1	95% CI
	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer	n	with cancer	SEER expected cancer				
<25	9	0	0.00027	39	1	0.00117	26	0	0.00078	20	0	0.0006	19	0	0.00057	25	0.00003	0.0005	(0.0003,0.0008)
26-35	14	1	0.00182	6	0	0.00078	17	0	0.00234	21	0	0.00273	19	0	0.00247	30	0.00013	0.0032	(0.0020,0.0045)
36-45	15	5	0.0111	11	1	0.00814	12	1	0.00888	18	2	0.01332	26	2	0.01924	40	0.00074	0.0285	(0.0180,0.0403)
46-55	14	3	0.02772	13	4	0.02574	31	2	0.06336	30	2	0.0594	13	1	0.02574	50	0.00198	0.1135	(0.0728,0.1580)
56-65	21	6	0.05859	21	5	0.05859	40	5	0.11439	11	5	0.03069	12	3	0.03348	60	0.00279	0.2392	(0.1574,0.3232)
66-75	5	1	0.02165	16	7	0.06928	37	5	0.16021	11	0	0.05629	20	2	0.0866	70	0.00433	0.3983	(0.2723,0.5163)
76+	6	2	0.0267	13	1	0.05785	28	1	0.1246	2	1	0.0089	13	0	0.05785	80	0.00445	0.5498	(0.3905,0.6804)

* Probability of having a pathogenic CDH1 variant is calculated using relationship to known carriers for ungenotyped individuals

eFigure 1. Germline Pathogenic Variants Identified



Sequence variants are designated by color coded symbols: ▲ = canonical splice variants; ● = frameshift and nonsense variants (nonsense mediated decay predicted to occur); ◆ = cryptic splice variants; ▬ = small deletion spanning an exonic/intronic boundary, and ● = frameshift and nonsense variants (nonsense mediated decay predicted to not occur). Each variant or cDNA position with more than one observation is designated by vertical stacking. Large deletions are designated by a black line while duplications are designated by a red line.