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Why Primary Tumours/Malignancies of the Nerve Cells are so rare?

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Supplementary

Database: M	Database: Medline (via OVID)								
Search	Search terms:	Number of							
number:		results							
#1	(tumor OR tumour)	2046342							
#2	#1 AND (CNS OR central nervous system)	27773							
#3	#1 AND (PNS OR peripheral nervoussystem)	4131							
#4	(cell cycle reentry) AND (DNA repair)	22							
#5	#4 AND neuron	0							
#6	(tumor suppressor gene OR tumoursuppressor gene)	21408							
#7	PTEN AND development AND mutation	887							
#8	#6 AND #7	116							
#9	#6 AND #7 AND (#2 OR #3)	3							
#10	Lymph AND lymphatic vessel	1465							
#11	#10 AND (#2 OR #3)	1							
#12	Rare AND syndrome AND mutation AND germline	1199							
#13	#12 AND #1	686							
#14	#12 AND #1 AND (glioma OR glioblastoma)	21							
#15	(Brain AND (#1 OR cancer)) AND ("incidence rate" OR "mortality rate") ANDrare	90							
#16	#5 OR #9 OR #11 OR #14 OR #15	115							

Database: Scopus

Search	Search terms:	Number of
number:		results
#1	TITLE-ABS-KEY (tumor OR tumour)	3667636
#2	#1 AND (CNS OR "central nervous system")	71952
#3	#1 AND (PNS OR "peripheral nervoussystem")	10597
#4	TITLE-ABS-KEY ("cell cycle re-entry" AND "DNA repair")	25
#5	#4 AND neuron	9
#6	TITLE-ABS-KEY ("tumor suppressor gene"OR "tumour suppressor gene")	83581
#7	TITLE-ABS-KEY (PTEN AND development AND mutation)	1691
#8	#6 AND #7	471
#9	#6 AND #7 AND (#2 OR #3)	22
#10	TITLE-ABS-KEY (Lymph AND lymphatic vessel)	18585
#11	#10 AND (#2 OR #3)	55
#12	TITLE-ABS-KEY (Rare AND syndrome AND mutation AND germline)	2000
#13	#12 AND #1	1469
#14	#12 AND #1 AND (glioma OR glioblastoma)	62
#15	TITLE-ABS-KEY ((Brain AND (#1 OR cancer)) AND ("incidence rate" OR "mortality rate")AND rare)	331
#16	#5 OR #9 OR #11 OR #14 OR #15	477
Appendix 1. S	earch terms generated into a search strategy using key terms	mentioned.
Database: Wel	o of Science	
Search number:	Search terms:	Number of results
#1	(tumor OR tumour)	2009822
#2	#1 AND (CNS OR "central nervoussystem")	38582
#3	#1 AND (PNS OR "peripheral nervous system")	1646
#4	"cell cycle re-entry" AND "DNA repair"	20
#5	#4 AND neuron	7
#6	"tumor suppressor gene" OR "tumoursuppressor gene"	32868
#7	PTEN AND development AND mutation	1481
#8	#6 AND #7	554
#9	#6 AND #7 AND (#2 OR #3)	14
#10	Lymph AND lymphatic vessel	4671
#11	#10 AND (#2 OR #3)	10
#12	Rare AND syndrome AND mutation AND germline	1952

#13	#12 AND #1	1218
#14	#12 AND #1 AND (glioma OR glioblastoma)	32
#15	(Brain AND (#1 OR cancer)) AND ("incidence rate" OR	103
	"mortality rate")	
	AND rare	
#16	#5 OR #9 OR #11 OR #14 OR #15	165

Appendix 2. Search strategy generated in order to perform literature search.

(Cell cycle re-entry AND DNA repair AND neuron) OR ((pten AND development AND mutation AND (tumor suppressor gene OR tumour suppressor gene)) AND (((tumor OR tumour) AND (cns OR central nervous system)) OR ((tumor OR tumour) AND (pns OR peripheral nervous system)))) OR ((lymph AND lymphatic AND vessel) AND (((tumor OR tumour) AND (cns OR central nervous system)) OR ((tumor OR tumour) AND (pns OR peripheral nervous system)))) OR ((rare AND syndrome AND mutation AND germline) AND (tumor OR tumour) AND (glioma OR glioblastoma)) OR ((Brain AND (tumor or tumour OR cancer)) AND (incidence rate OR mortality rate) AND rare)

Theme: Regeneration and proliferation ability of nerve cells									
Author and year	Name of paper	St ud y de sig	Aim of paper	Methods	Key findings	Contributio n in current study	Critical analysis (+/-)		
		n							
Tomashe vski, et al. 2010	Cyclin C- depende nt cell cycle entry is required for activatio n of nonhom olog ous end joining DNA repair in postmito tic neurons	Re tro spe cti ve no n- ran do mi sed co hor t stu dy	Understand the mechanisms underlying DNA repair in terminally differentiate d neurones. Alongside the stimulatory factors triggering cell- cycle re- entry of these postmitotic neurones to undergo DNA damage response.	Cortical neurone cell cultures were obtained from E18 Sprague- Dawley rats, cells were seeded onto dishes. Cortical neurones were treated with hydrogen peroxide (H ₂ O ₂) to induce DNA damage	H ₂ O ₂ induces repairable double- strand DNA breaks in terminally differenti ated neurones. ·Neurone s transitioni ng from G0 to G1 exposes them to double- strand DNA	The ability of postmitotic neurons to repair damaged DNA by re- entering the cell-cycle without producing two daughter cells indicates adaptations to avoid oncogenic mutations in developing in neurones	Strengths: Saw consistent results with DNA repair using NHEJ. Positive and negative controls were used in immunoblo tting analysis. Specific neuronal markers were used to identify		

					Cells were	breaks	Repairing	areas of
					fixed	where	DNA	DNA repair
					stained with	proteins	damage	taking
					DNA-	involved	using NHEJ	place via
					binding dye	in	C	NHEJ.
					to calculate	regulating		Limitations
					number of	cell cycle		: Using rat
					apoptotic	are		models
					nuclei.Neur	activated		may not be
					onal	too early.		translatable
					markers	5		results into
					were used			human
					to see sites			studies.
					of non-			Non-
					homologous			randomised
					end joining			retrospectiv
					(NHEJ)			e study
					pathway			increases
					activation in			risk of bias.
					neurones.			Study was
					This was			only
					seen using			focused on
					immunofluo	,		postmitotic
					rescence			neurones
					analysis.			and could
					Immunoblot	;		have
					ting			benefited
					measures			from
					expression			
					of Cyclins			
					following			
					exposure of			
					neurones to			
					H_2O_2 and			
					transfected			
					with either			
					cyclin or			
					control			
					siRNA in			
					order to			
					detect cell-			
					cycle			
					progression.			ļ
Tomashe	Cyclin	Re	Understand	• (Cortical	• H ₂ O ₂	• The ability	Strengths:
vski, et	C-	tro	the	ne	eurone cell	induces	of	Saw
al. 2010	depende	sp	mechanism	cι	ultures were	repairable	postmitotic	consistent

nt cell	ect	S	obtained	double-	neurons to	results with
cycle	ive	underlying	from E18	strand DNA	repair	DNA repair
entry is	no	DNA repair	Sprague-	breaks in	damaged	using
required	n-	in	Dawley rats,	terminally	DNA by re-	NHEJ.
for	ran	terminally	cells were	differentiate	entering the	Positive
activatio	do	differentiate	seeded onto	d neurones.	cell-cycle	and
n of	mi	d neurones.	dishes.	• Neurones	without	negative
nonhom	se	Alongside	Cortical	transitionin	producing	controls
olog ous	d	the	neurones	g from G0	two	were used
end	co	stimulatory	were treated	to G1	daughter	in
joining	ho	factors	with	expose	cells	immunoblo
DNA	rt	triggering	hydrogen	them to	indicates	tting
repair in	stu	cell-cycle	peroxide	double-	adaptations	analysis.
postmito	dy	re- entry of	(H_2O_2) to	strand DNA	to avoid	Specific
tic		these	induce DNA	breaks	oncogenic	neuronal
neurons		postmitotic	damage.	where	mutations in	markers
		neurones to	 Neuronal 	proteins	developing	were used
		undergo	markers were	involved in	in neurones.	to identify
		DNA	used to see	regulating	 Repairing 	areas of
		damage	sites of	cell cycle	DNA	DNA repair
		response.	non-	are	damage	taking
			homologous	activated	using NHEJ	place <i>via</i>
			end joining	too early.	machinery	NHEJ.
			(NHEJ)	•	enables	Limitations
			pathway	Terminally	neurones to	: Using rat
			activation in	differentiate	stay	models
			neurones.	d neurones	plentiful in	may not be
			This was	can induce	their	translatable
			seen using	NHEJ	abundance	results into
			ımmunofluor	following	due to lack	human
			escence	detection of	of	studies.
			analysis.	double-	regenerating	Non-
			•Immunoblot	strand DNA	abilities.	randomised
			ting	breaks.		retrospectiv
			measures	• Post-		e study
			expression of	mitotic		increases
			Cyclins	neurones		risk of bias.
			following	forced GI		Study was
			exposure of	entry		only
			neurones to	Induces		locused on
			$\Pi_2 \cup_2$ and the stand			posimitotic
			with aith an	activation		neurones
			with either	regardless		and could
			cyclin or	OI DINA		have
			control	damage.		benefited
	1		SIKINA IN			from

				order to			experiment
				detect cell-			ing
				cycle			alongside
				progression.			different
				1 0			differentiat
				• Cells were			ed levels of
				fixed stained			neurones to
				with DNA-			see full
				binding dye			effect of
				to calculate			DNA repair
				number of			mechanism
				apoptotic			s. Did not
				nuclei.			provide
							understandi
							ng of the
							reasons
							behind
							cells
							undergoing
							DNA repair
							or
							undergoing
							apoptosis
							following
							DNA 1
							damage
Cincert	F	D .	T	T	. 11. 1.		detection.
G_{1} G_{1} G_{1} G_{1} G_{1} G_{2} G_{1} G_{2} G_{1} G_{2} G_{2	Expressi	Ke tro	To explore	• Itssues	• High	• Evaluation	Strengths:
al. 2000	DTEN	tro	PIEN	from whole	PIEN	Explanation	in high
	PIEN tumour	sp	throughout	humon	expression was seen in	that DTEN	in nigh
		ivo	human	mullian	tissues	nlaus in	of DTEN in
	or		developmen	and footuses	directly	plays III	the CNS
	nrotein	ho	tusing	(2)	involved in	neuronal	and PNS
	during	rt	monoclonal	(2) (following	CS and	tissues in	have been
	human	stu	antibodies	abortion)	BRR	developmen	supported
	develop	dv	As well as	fixed and	diseases	t and its	by RNA in
	ment	ay	examining	mounted	such as the	involvement	situ
			the	• Specific	skin.	in regulation	hybridisati
			relationship	monoclonal	thyroid. and	of the cell-	on
			with	antibodies	CNS.	cvcle.	experiment
			germline	recognising	• The	migration.	s. Specific
			PTEN	PTEN were	highest	and	monoclonal
			mutations	created and	expression	apoptosis.	antibodies
			with the	Western	ofPTEN	High	to PTEN
			genetic	Blotting was	was seen in	expression	show clear

	conditions	performed to	the CNS	in nerve	areas and
	Cowden's	indicate	and PNS	plexus and	tissues with
	syndrome	bands of	which was	enteric	high or low
	(CS) and	PTEN	maintained	nerves were	expression.
	Bannayan-	expression.	throughout	seen to	Explored
	Riley-	This was	the	show	different
	Ruvalcaba	compared	developmen	involvement	systems
	(BRR)	against	t process.	of PTEN in	among the
	syndrome.	controls.	• PTEN is	peripheral	body for
		• Further	highly	nerves.	examining
		immunohisto	expressed		different
		chemistry	in the		expression
		was	gastrointesti		levels.
		performed to	nal system		Foetuses
		classify	and thyroid		and
		expression as	gland.		embryos
		absent, weak,	• Moderate-		are
		moderate or	h1gh		reasonable
		strong.	expression		for
			of PTEN in		examining
			thymus		developme
					ntal .
					expression
					of PIEN in
					embryogen
					esis.
					Limitations
					: Small
					(7 somplos)
					(7 samples)
					data may
					uata may
					representati
					ve of
					nonulation
					Samples
					were
					embryos
					and
					foetuses
					expression
					may not be
					representati
					ve into
					adult form.

							Retrospecti
							ve non-
							randomised
							study
Crocetti,	Epidemi	Pr	Collectively	•	• 27,700	from this	Strengths:
et al.	ology of	os	analyse data	Establishmen	new "rare"	study to	This paper
2012	glial and	pe	to	t of	CNS cases	compare	combined
	non-	cti	determine	categories of	are	three types	data from
	glial	ve	incidence,	tumours	estimated to	of nerve cell	numerous
	brain	co	prevalence,	depending on	be	tumours	different
	tumours	ho	and survival	clinical	diagnosed	(astrocytom	registries
	in	rt	rate of a	management	every year	a's,	across
	Europe	stu	group of	and patient	in EU27.	oligodendro	Europe to
		dy	rare CNSTs.	referral	• Rare	glioma's	provide
				structure.	CNSTs	and	representati
				• Glial	were	ependymal	ve data on
				tumours were	marginally	tumours) to	incidence
				categorised	more	compare the	and
				depending on	frequent in	prevalence	prevalence
				WHO	men than	of these	rates of
				classification	women.	tumours in	CNS1s.
				·	Astrocytom	gender as	They
				• Data was	a's were the	well as age.	achieved
				extracted	most	I his	their aim
				1rom 44,94 /	common	supported	and
				rare types of	CNSI al a	the	separated
				diagnosod	1210 01 4.0	that the	CNSTs into
				batwaan	and their	tumours	cub
				1005 2002		uniours	sub-
				1995-2002 from	was most	commonly	depending
				different	nrevalent	in the elder	on their
				countries in	in UK and	nonulation	malignanci
				Furone	Ireland	in certain	es
				Europe.	n ciana.	CNSTs	Limitations
						011015.	· Only
							European
							not
							worldwide.
							Not all
							CNSTs,
							only a
							selected
							few of glial
							tumours to
							compare

							against non-glial CNSTs. Greater numbers of astrocytic tumours (86.9%) were examined in comparison to choroid plexus carcinomas (0.1%).
Hu, et al. 2020	Meninge al lymphati c vessels regulate brain tumor drainage and immunit y	Re tro sp ect ive co ho rt stu dy	Exploring the role of meningeal lymphatic vessels (MLVs) in drainage of brain tumours.	 Retroviral vectors were created overexpressi ng GFP and VEGF-C in GL261 and B16 (glioma and melanoma markers) cells for detection. Tumour cells were transplanted into mice, located 2 mm lateral to bregma and 3 mm deep to dura. Deep and superficial lymph nodes were removed following ligation of collecting 	Dorsal MLVs undergo vast remodelling following glioma infiltration and are essential for dendritic cell trafficking towards deep cervical lymph nodes • Basal MLVs are susceptible to damage with increasing age • Dendritic cells showed reduced trafficking	Understandi ng the contribution of the lymphatic vessels and lymph nodes in harbouring immune cells to destroy tumour cells in the CNS. In particular dendritic cell role in stimulating immune responses following activation in MLVs.	Strengths: provide prospects for therapeutic opportuniti es targeting MLVs and cervical lymph nodes. Studying both basal and dorsal MLVs allowed differences to be seen rather than assuming the similar responses to tumour cell infiltration. Limitations : Mice models were used where

				lymphatic	ability from		conclusions
				vessels.	tumour		in human
				• MRI and	tissue to		model may
				immunostain	deep		be
				ing were	cervical		inconsisten
				performed to	lymph		t with these
				detect	nodes		results and
				tumour	where		the data
				growth	dorsal		may be
				8	MLVs were		incomparab
					deformed.		le.
Castricon	NK	Pr	To explore	• Tumour	Stem cell	Understandi	Strengths:
i et al	Cells	05	the	cells were	cultured	ng the	Only GBM
2009	Recogni	ne	differentiati	separated	GBM cells	ligand-	natients
2009	ze and	cti	on ability	from 9	tested	recentor	with
	Kill	ve	tumorigenic	natients with	positive for	interactions	typical
	Human		ity and	GBM •	neural stem	hetween NK	characterist
	Glioblas	ho	expression	These GBM	cell	cells and	ics of GBM
	toma	rt	of neural	cells were	markers but	GBM cells	were
	Cells	etu	stem cell	cultured in	only 15%	This aided	included
	with	dy	markers in	vitro in stem	of cells	in	this
	Stem	uy	stem cell	cell medium	showed	understandi	reduces the
	Call		sultured	and woro	differentiati	understand	abanaa of
	Liko		CPM colla	tostad for	on	ng me tote	chance of
	Duan anti		UDIVI CEIIS.	rested for			data
	rioperu		in addition,		properties		uala
	es		exploring	cell markers	to normal	system m	Inclusion.
			stelli- cell	allu		tumour	riovides
			CDM coll	to lugic by		cumouths and	opportuniti
				NW aslla	Cells.	growins and	
			susceptionit	INK CEIIS.	• Stem cen	destroying	therapeutic
			y to lysis by	tumorigenicit	CDM	them using	approaches
			autologous	y. • Flow		INK Cells.	
			and	cytoffuorimet	snowed	Provided an	created
			allogenic	ric	tumorigenic	understandi	using
			INK CEIIS.		potential	ng or the	activated
					where furth or	roles of	INK Cells
					iniantiana	various	against
					injection of	figands on	UBIVI.
					inese cells	ine surface	Limitation:
					developed	OI INK Cells	
					gliomas in	1n 1'	sample size
					new mice.	responding	(9 patients,
					• Stem cell	to pathogens	/ males, 2
					cultured	and	temales),
					GBM cells	tumours. In	might be
					are	particular	unrepresent

					vulnerable	the role of	ative of the
					to NK lytic	NKp46 and	population
					abilities	DNAM-1	of GBM
					(both	receptors in	patients.
					autologous	the efficient	Portions of
					and	killing of	this study
					allogenic	GBM cells.	were
					NK cells).	This is	performed
					• Key	important	in vitro
					receptors	because	where
					were	DNAM-1 is	results are
					analysed	frequently	less likely
					for specific	detected in	to be
					ligand	most cancer	transferable
					interactions	cell lines	to in vivo
					with stem	including	experiment
					cell	GBM and	s. Only
					cultured	neuroblasto	studies
					GBM cells	mas.	GBM
							rather than
							other types
							of CNSTs
							such as
							astrocytom
							as.
							No
							financial
							contributio
							ns or
							conflicts of
							interest.
Malmer,	Microsat	Re	То	• Paraffin-	• No MSI	Contributed	Strengths:
et al.	ellite	tro	investigate	embedded	was found	to the fact	Mentioned
2001	Instabilit	sp	the	tumour DNA	in	that nerve	that their
	y, PTEN	ect	presence of	and blood	association	cell tumours	results
	and p53	ive	germline	DNA	with any of	are so rare	were
	Germlin	co	mutations	samples were	the 35	due to the	correspondi
	e	ho	in p53 and	taken from	tumours.	fact that	ng to
	Mutatio	rt	PTEN in	25 families	• A repeated	germline	similar
	ns in	stu	related	(3 patient	polymorphi	mutations	literature.
	Glioma	dy	family	samples per	sm was	which	All groups
	Families		members	family) who	detected at	increased	were
			where two	suffer from	exon 4	prevalence	treated
			or more	gliomas.	codon 7 in	of nerve cell	with the
			members	• PTEN	eight	tumours	same
			suffer from	analysis was	patients.	have not	treatment

			glioma	achieved	Mutations	been	to detect
			tumours.	with PCR	were not	detected in	mutations
			Exploring	with primers	shown	any of these	in the
			whether	to PTEN •	associated	patients.	genes
			microsatelli	p53 exons	with PTEN	Also	mentioned.
			te	were	in any of	indicates the	Limitations
			instability	screened in	the cases.	varying	: Tumour
			(MSI) is	blood DNA		presentation	samples
			associated	for exon		associated	were
			with glioma	mutations		with nerve	paraffin-
			sufferers.	(exons 2-9)		cell tumours	embedded
				<i>via</i> temporal		in terms of	which
				temperature		types of	doesn't
				gradient		genetic	represent
				electrophores		mutations.	fresh tissue
				is.		Showed the	which
				MSI was		types of	could have
				tested with		syndromes	displayed
				two markers:		associated	different
				BAT 25 and		with gene	results. No
				BAT		mutations in	controls
				26.		TP53,	were used
						PTEN and	to compare
						NF1 genes.	mutation
							levels in
							gliomas to.
Khazaei,	The	Pr	Investigate	• Data for the	• The total	Provided	Advantages
et al.	associati	os	the	morbidity	number of	information	: Using
2020	on	pe	relationship	and mortality	cancer	for whether	four
	between	cti	of brain	rates for	cases found	brain	different
	incidenc	ve	tumours	brain cancer	for both	tumours	cancer
	e and	cas	morbidity	were taken	sexes are	have	registries
	mortalit	e	and	from the	18,078,957	increased	allowed the
	y of	stu	mortality	World Bank	in which	likelihood	researchers
	brain	dy	rates with	for Cancer.	brain	of	to get the
	cancer		the	 Morbidity 	tumours	developing	most
	and		socioecono	rates to relate	represented	depending	accurate
	human		mic	age and	296,851	on ethnicity,	incidence
	develop		developmen	gender were	(1.64% of	gender, age,	rates of
	ment		t of	calculated	total types	availability	brain
	index		countries by	using the	of cancer). •	to	tumours in
	(HDI):		measuring	incidence	The	healthcare.	countries.
	an		their human	rates reported	continent		Prospective
	ecologic		developmen	in four	with the		study
	al study		t index	separate	highest		Limitations
			(HDI).	cancer	incidence		: Certain

		registries of	rate was	lower
		countries	seen in Asia	income
		until 2018.	and the	countries
		 Mortality 	lowest seen	do not have
		rates were	in Oceania.	the
		estimated		healthcare
		using four		facilities to
		separate		report the
		registries.		incidence
		• HDI was		rate of
		calculated		brain
		using an		tumours.
		index		This means
		depending on		that not all
		three criteria:		of the data
		education,		here is
		life		representati
		expectancy		ve of
		and good		"worldwide
		standards of		trends".
		living. This		Averages
		created a		were
		scale for		assumed in
		measuring		the
		HDI for the		methods
		countries		section.
		used in this		
		study.		

Appendix 3: Results following a detailed search strategy creating a shortlist of papers to analyse in the literature synthesis. Various categories have been identified to give detailed explanations as to why each research paper has been included in this literature review. Search strategies on different databases performed between 14/03/22 – 18/05/22

	G		Or second (P. MARCHINA	Rectioner - Toppe	e a Troneig .	THE APP	10010	Louise.		
earth	dramatik.	Reeds Mallandla WyWelspies Visiall's ITF light + War's New									
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Appendix 3. Results from literature search on Medline (Ovid) and Scopus to generate publications to undergo criteria-based selection process and critical analysis.