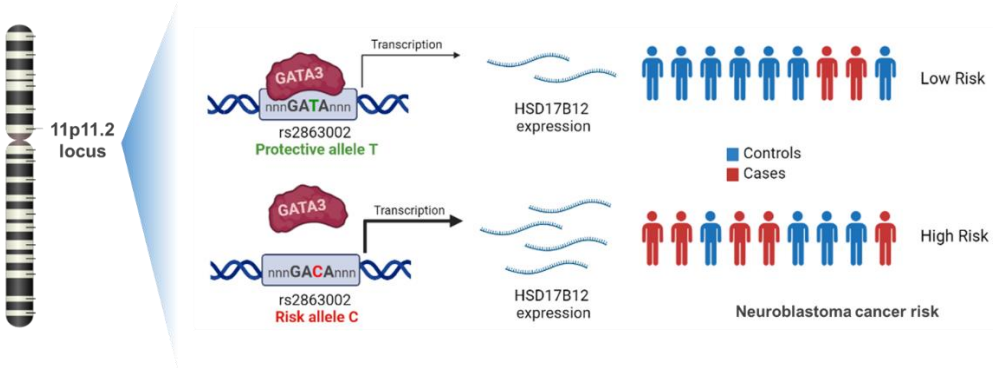
UNIVERSITY OF NAPLES FEDERICO II

DOCTORATE IN
MOLECULAR MEDICINE AND MEDICAL BIOTECHNOLOGY

XXXV CYCLE

Teresa Maiorino

Functional characterization of 11p11.2 risk locus identifies *HSD17B12* as neuroblastoma susceptibility gene involved in lipid metabolism



2019-2023

UNIVERSITY OF NAPLES FEDERICO II

DOCTORATE IN
MOLECULAR MEDICINE AND MEDICAL BIOTECHNOLOGY

XXXV CYCLE

Functional characterization of 11p11.2 risk locus identifies *HSD17B12* as neuroblastoma susceptibility gene involved in lipid metabolism

Tutor
Prof. Mario Capasso

Candidate
Teresa Maiorino

2019-2023

Table of contents

List of Abbreviations

AC	acylcarnitines
ADRN	adrenergic
ALA	α-linolenic acid
ASCR	autologous stem cell rescue
ATAC	Assay for Transposase-Accessible Chromatin
ATP	Adenosine triphosphate
CCHS	congenital central hypoventilation syndrome
CE	cholesterol esters
Cer	ceramides
CHD	congenital heart diseases
ChIP	chromatin immuno-precipitation
ChIPseq	chromatin immuno-precipitation sequencing
CI	confidence intervals
CIN	chromosome instability
CNV	copy number variation
COJEC	cisplatin (C), vincristine (O), carboplatin (J), etoposide (E), and cyclophosphamide (C)
CRC	core regulatory circuitry
DAG	diacylglycerol
DEG	differentially expressed genes
DFMO	difluoromethylornithine
DSH	DNase-I hypersensitivity
EBRT	external beam radiotherapy
EFS	event-free survival
eQTL	expression quantitative trait loci
ER	endoplasmic reticulum
FA	fatty acid
FABPpm	fatty acid-binding protein
FATP	fatty acid transport proteins
FDR	false discovery rate
GO	Gene Ontology
GO BP	Gene Ontology database of Biological Processes
GSL	glycosphingolipids
GWAS	Genome Wide Association Study
HexCer	hexosylceramides
Hi-C	High-Throughput Chromatin Conformation Capture
HR	high-risk
HVA	homovanillic acid

HydCer	hydroxyCeramides
IDRF	image-defined risk factors
INRGSSo INRG	International Neuroblastoma Risk Group Staging System
INSS	international neuroblastoma staging system
LA	linoleic acid
LCFA	long chain fatty acids
LC-MS/MS	Liquid chromatography–mass spectrometry
LD	linkage disequilibrium
lncRNA	long non coding RNA
LOH	loss of heterozygosity
LPC	lysophosphatidylcholine
MES	mesenchymal
mtDNA	mitochondrial DNA
MTT	3-(4,5-Dimethylthiazol-2l),5-Diphenyltetrazolium Bromide
MUFA	monounsaturated fatty acids
NB	neuroblastoma
NCC	neural crest cell
OR	Odds ratios
OS	overall survival
PA	phosphatidic acid
PC aa	acyl-acyl phosphatidylcholine
PC ae	acyl-alkyl phosphatidylcholine
PCR	polimerase chain reaction
PE	phosphatidylethanolamine
PG	phosphatidylglycerol
PGE2	Prostaglandin E2
PS	phosphatidylserine
PUFA	polyunsaturated fatty acids
qRT-PCR	quantitative real time PCR
RNAseq	RNA sequencing
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SIOPEN	Society of Pediatric Oncology Europe Neuroblastoma Group
siRNA	small interfering RNA
SM	sphingomyelins
SNP	single mucleotide polimorphism

TAG	triacylglycerol
TCA	tricarboxylic acid cycle
UPR	unfolded protein response
VIP	Variable Importance in Projection
VLCFA	very long chain fatty acids
VMA	vanillylmandelic acid

ABSTRACT

Genome-wide association studies (GWAS) have given an essential contribution to the study of neuroblastoma genetic basis by identifying common risk variants that activate cancer-related biological processes. The risk locus 11p11.2 detected in our previous GWAS on 2101 neuroblastoma cases and 4202 controls of European American origin, remains to date functionally unexplored.

The present study aims to functionally characterize the 11p11.2 neuroblastoma predisposition locus by evaluating how its regulatory variant and target gene may affect neuroblastoma development.

To detect functional variants, we annotated candidate SNPs inside the 11p11.2 locus using data regarding chromatin accessibility, epigenetic features and presence of transcription factor binding motifs from neuroblastoma cell lines, and identified rs2863002 as the functional variant of the locus 11p11.2. The enhancer activity of the regulatory variant was validated by *in vitro* luciferase assays, demonstrating that the C allele of rs2863002 acts as enhancer. Searching for the presence of transcription factors binding sites in the genetic region surrounding the candidate variant, we found that the rs2863002 C allele alters a GATA3 transcription factor binding motif and we assessed GATA3 differential allele binding through *in vitro* ChIP q-PCR experiments.

Public Hi-C data from neuroblastoma cells and expression quantitative trait loci (eQTL) analysis were used to identify the most likely target gene of the locus activity. Then, to evaluate the target gene proto-oncogenic role in neuroblastoma, we correlated gene expression to clinical and prognostic parameters. The C allele of rs2863002 showed to be associated with increased *HSD17B12* expression and risk of neuroblastoma development, and higher *HSD17B12* expression correlated with poor prognostic features and poor survival in neuroblastoma tumors. *In vitro* proliferation and invasion cellular assays following *HSD17B12* silencing were performed, demonstrating that

HSD17B12 silencing significantly impairs proliferation and invasion capacities of neuroblastoma cells.

Finally, the biological activity of *HSD17B12* was investigated by targeted Lipidomic analysis and RNA-sequencing. Impairment of *HSD17B12* expression proved to alter lipid metabolism in neuroblastoma cells, leading to a decrease in lipid species related to energy production and to changes in membranes composition and properties. This lipid metabolic stress seemed to activate in neuroblastoma cells silenced for *HSD17B12* different response processes, such as Interferon-induced inflammation and Endoplasmic Reticulum stress response.

In conclusion, the functional investigation of the 11p11.2 risk locus supports the role of *HSD17B12* as a susceptibility gene in neuroblastoma. We dissected the molecular mechanism by which the candidate variant rs2863002 at 11p11.2 risk locus regulates *HSD17B12* oncogenic expression. Moreover, our results indicated that *HSD17B12* promotes neuroblastoma tumorigenesis by altering the availability of lipid energy sources and the properties of cellular membranes through its involvement in lipid metabolism.

Altogether, the present study demonstrated that post-GWAS strategies are essential for the identification of causal functional variants at cancer-risk loci and for the detection of predisposition genes with key roles in tumor biology.

1. BACKGROUND

1.1 Neuroblastoma

1.1.1 Clinical presentation and pathogenesis

Neuroblastoma (NB) is the most common extra cranial solid tumor in childhood and accounts for approximately 15% of all pediatric oncology deaths (Takita 2021). The prevalence of this tumor is 10.7 cases per million children under 15 years of age (Colon and Chung 2011) and approximately 700 new cases of neuroblastoma each year in the United States (Chung et al. 2021). Most children are diagnosed under the age of five years, with a median age at diagnosis of 17 months (Ponzoni et al. 2022, Lerone et al. 2021). Rarely, there are cases observed in utero or in patients older than 19 years, with much poorer outcomes in this age group (London et al. 2005, Zeineldin, Patel, and Dyer 2022).

Neuroblastoma is also classified as embryonic tumor, as it derives from the malignant transformation of neural crest-derived precursors of the sympathetic nervous system during the fetal life (Aygun 2018, Takita 2021). During embryogenesis, neural crest cells undergo an epithelial-mesenchymal transition acquiring the ability to delaminate, migrate, and differentiate into various cell types (**Fig. 1.1**) (Cheung and Dyer 2013). In physiological conditions, sympatho-adrenal progenitor cells differentiate to form sympathetic ganglion cells and adrenal chromaffin cells, the catecholamine-secreting cells of the adrenal medulla (L'Abbate et al. 2014).

There is extensive evidence that dysregulation of the sympatho-adrenal lineage precursors migration and cell differentiation result in neuroblastoma initiation and progression (Takita 2021). Recently, transcriptional profiling of NB tumors has identified two distinct cell identities that represent divergent differentiation states and exhibit distinct expression patterns in core regulatory circuitry-related genes (Takita 2021): the more undifferentiated mesenchymal (MES) subtype and the committed adrenergic (ADRN) one, able to interconvert

by epigenetic reprogramming and to confer intra-tumoral heterogeneity and high plasticity to neuroblastoma (Ponzoni et al. 2022).

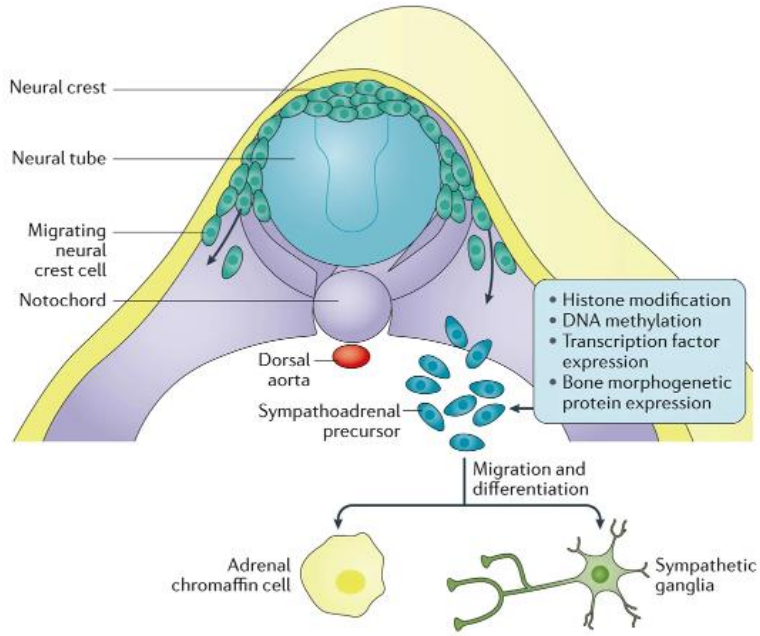


Figure 1.1 Neuroblastoma developmental origin. Neural crest cells can give rise to many cell types and anatomical structures. They undergo epithelial-to-mesenchymal transition, which enables neural crest cells to delaminate and migrate from the neural tube. Histone modifications, DNA methylation and the expression of bone morphogenetic proteins and transcription factors regulate the delamination process. Some neural crest cells migrate to the dorsal aorta, where they differentiate into sympatho-adrenal progenitor cells, which eventually give rise to cells of the peripheral nervous system, including sympathetic ganglia and the adrenal gland, the main sites in which neuroblastoma arises. *Adapted from Matthay et al. Neuroblastoma Nat Rev Dis Primers 2, 16078 (2016).*

Tumors can arise in adrenal glands or in sympathetic ganglia with metastatic sites in bone marrow, lymph nodes, bone, liver, and orbital sites (**Fig. 1.2**). (Lerone et al. 2021, Matthay et al. 2016) Clinical symptoms vary depending on the location of the primary tumor and may include an abdominal mass, abdominal pain, respiratory distress, or neurological symptoms from spinal cord involvement (Angstman, Miser, and Franz 1990, Chung et al. 2021). In addition to the early age of onset, these neuroendocrine tumors exhibit unique clinical

features as the high frequency of metastatic disease at diagnosis and the tendency for spontaneous regression of tumors in infancy (Matthay et al. 2016). Indeed, neuroblastoma prognosis ranges from spontaneous regression to progression, metastasis, and death with 5-year overall survival of more than 90% in the low-risk group, and about 40–50% in high-risk (HR) group patients (Lerone et al. 2021, Bosse and Maris 2016, Matthay et al. 2016).

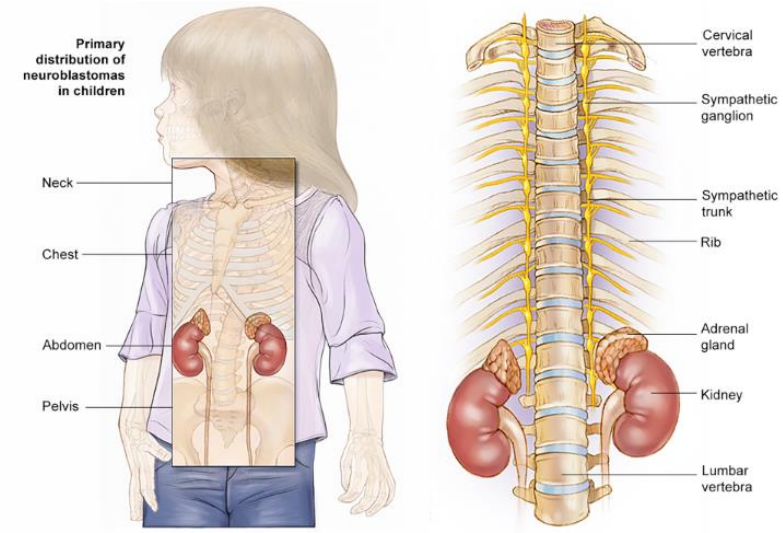


Figure 1.2. Clinical Presentations of Neuroblastoma. *Adapted from American Society of Clinical Oncology 2005.*

1.1.2 Diagnosis and staging

Neuroblastoma diagnosis requires multiple tests, including laboratory tests, radiographic imaging and histological assessment of the tumor (Matthay et al. 2016). Biopsy of the primary tumor or metastatic lesions is generally required to establish the diagnosis, although, when the risk of tumor biopsy is considered unacceptable, diagnosis can be made based on bone marrow involvement and elevated urinary catecholamines or catecholamine metabolites, including dopamine, homovanillic acid (HVA) and/or vanillylmandelic acid (VMA) (Chung et al. 2021). Tumor stage and biology are determined at diagnosis, following which patients are stratified for treatment according to the different risk groups (Matthay et al. 2016).

Patients are classified in different risk groups defined by several prognostic factors including age at diagnosis, stage, histological features, and molecular alterations (Ponzoni et al. 2022, Matthay et al. 2016). The international neuroblastoma staging system (INSS), established in 1989, classifies neuroblastoma patients into five stages, principally on the basis of extent of surgical excision at diagnosis and metastases (Takita 2021). Stages 1 and 2 show distinguished localized tumors, stage 3 is characterized by an advanced loco-regional disease, and stage 4 or 4s comprise metastatic tumors (**Table 1.1**) (Smith et al. 1989, Takita 2021).

Table 1: The international neuroblastoma staging system (INSS)	
Stage 1	Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive).
Stage 2A	Localized tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically.
Stage 2B	Localized tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumour infiltrating across the midline (vertebral column) with or without regional lymph node involvement; or localized unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S).
Stage 4S	Localized primary tumour (as defined for stage 1, 2A or 2B), with dissemination limited to skin, liver and/or bone marrow (limited to infants <1 year of age).

Table 1.1 The international neuroblastoma staging system (INSS)

More recently, additional biological features and molecular markers have been introduced to better define the risk groups and to predict prognosis and disease recurrence (Lerone et al. 2021). The challenge has been to identify children who may benefit from treatment reduction instead of intensified therapies.

To this aim, the European International Society of Pediatric Oncology, validated a set of surgical risk factors based on radiographic characteristics, that could be used to assess tumor resectability and risk of developing postoperative complications (Brodeur and Seeger 1986). These characteristics, renamed image-defined risk factors (IDRFs), were incorporated together with clinical and molecular criteria into the new International Neuroblastoma Risk Group Staging System (INRGSS or INRG) (**Table 1.2**). INRGSS classifies neuroblastoma in

four stages: localized disease without (L1) and with (L2) IDRFs, metastatic disease (M) and metastatic disease in very young children that is limited to specific sites (MS) (Chung et al. 2021, Takita 2021).

The INRG Task Force also developed the INRG Consensus Pretreatment Classification Schema for pretreatment risk stratification (Chung et al. 2021). In particular, the disease stage is combined with other prognostic factors, including age at diagnosis, pathology and genomic characterization (including *MYCN* amplification, 11q status and ploidy) to define pretreatment risk groups. This system enables patients to be grouped into very-low, low, intermediate or high-risk groups in terms of 5-year event-free survivals (Matthay et al. 2016, Chung et al. 2021). These risk groups can be used to assign treatment recommendations or assess a patient's eligibility for participation in investigational studies (Brodeur et al. 1987). Moreover, thanks to the higher resolution of modern genomic techniques and the integration of next-generation sequencing at a DNA and RNA level, it is likely that risk groups will be further refined based on the tumor molecular profile, leading to an increasingly personalized medicine (Matthay et al. 2016)

Table 2. International Neuroblastoma Risk Group Staging System (INGSS)

Risk group for treatment	INRG stage	IDRFs in primary tumor	Distant metastases	Age (month)	Histological category	Grade of differentiation	MYCN status	Genomic profile	Ploidy
Very-low	L1	Absent	Absent	Any	GNB nodular, NB	Any	–	Any	Any
	L1 or L2	Any	Absent	Any	GN, GNB intermixed	Any	–	Any	Any
	MS	Any	Present	<12	Any	Any	–	Favorable	Any
Low	L2	Present	Absent	<18	GNB nodular, NB	Any	–	Favorable	Any
	L2	Present	Absent	≧18	GNB nodular, NB	Differentiating	–	Favorable	Any
	M	Any	Present	<18	Any	Any	–	Any	Hyperdiploid
Intermediate	L2	Present	Absent	<18	GNB nodular, NB	Any	–	Unfavorable	Any
	L2	Present	Absent	≧18	GNB nodular, NB	Differentiating	–	Unfavorable	Any
	L2	Present	Absent	≧18	GNB nodular, NB	Poorly differentiated, undifferentiated	–	Any[a]	Any
	M	Any	Present	<12	Any	Any	–	Unfavorable and/or diploid	
	MS	Any	Present	12–18	Any	Any	–	Favorable	Any
	MS	Any	Present	<12	Any	Any	–	Unfavorable	Any
High	L1	Absent	Absent	Any	GNB nodular, NB	Any	+	Any	Any
	L2	Present	Absent	≧18	GNB nodular, NB	Poorly differentiated, undifferentiated	+	Any	Any
	M	Any	Absent	12–18	Any	Any	–	Unfavorable and/or diploid	
	M	Any	Present	<18	Any	Any	+	Any	Any
	M	Any	Present	≧18	Any	Any	Any	Any	Any
	MS	Any	Present	12–18	Any	Any	–	Unfavorable	Any
	MS	Any	Present	<18	Any	Any	+	Any	Any

[a]Some clinical trial group consider unfavorable pathology with Stage L2, over 18 months of age. GN, ganglioneuroma; GNB, ganglioneuroblastoma.

Table 1.2 International Neuroblastoma Risk Group Staging System (INGSS). *Adapted from Nakagawara, Japanese Journal of Clinical Oncology, (2018).*

1.1.3 Therapy

The choice of the proper therapeutic regimen is based on the risk classification of neuroblastoma. Non-high-risk NB is a heterogeneous group that comprises patients with non-*MYCN* amplified localized tumors but also patients with a metastatic disease. For this group the therapeutic regimen ranges from surgical resection to chemotherapy for patients developing a relapse after the resection or showing life or organ-threatening symptoms, such as spinal cord compression or respiratory compromise (Mertens et al. 2001).

In young infants with favorable biology, many tumors spontaneously regress without the need for treatment, even if they have metastatic disease (Matthay et al. 2016). The surgical resection or the merely observation are indicated for patients with small localized tumors, for which the overall survival (OS) is excellent with values greater than 95%. By contrast, the outcomes for high-risk patients remain poor although the many progresses over the years in the treatment strategy (Tolbert and Matthay 2018). Modern protocols, including induction chemotherapy, surgical resection, high-dose chemotherapy with autologous stem cell rescue (ASCR), external beam radiotherapy (EBRT), and immunotherapy or differentiating agents, have improved outcomes with 3-year survival rates now exceeding 60% (Chung et al. 2021). Past treatments that used less intensive chemotherapy resulted in 4-year survival rates of 10%-15% (Chung et al. 2021).

The standard regimen includes 4 consecutive steps: induction chemotherapy, local control, consolidation, and maintenance therapy. The most used induction regimen includes a combination of anthracyclines, platinum-containing compounds, alkylating agents and topoisomerase II inhibitors. The Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) has utilized a rapid COJEC regimen that consists in combinations of vincristine, carboplatin, etoposide, cyclophosphamide, and cisplatin (Smith and Foster 2018). The local control aims to prevent local recurrence of the disease and includes surgical resection and a cycle of irradiation to the primary site and other

sites of residual disease (Du et al. 2014). Consolidation therapy includes myeloablative chemotherapy and autologous stem cell rescue (ASCR) that confers to high-risk patients a statistically significant improvement in event-free survival (EFS) (Yalcin et al. 2013).

The use of a synthetic 13-cisretinoic acid, isotretinoin, has shown its efficacy as it reduces proliferation and induces differentiation in neuroblastoma cells (Matthay et al. 2009). More recently, the use of monoclonal antibody against the GD-2 ganglioside, a cell-surface marker expressed by NB cells, in combination with cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) have improved response rates for high-risk neuroblastoma (Yu et al. 2010, Takita 2021). Another modern approach includes the use of difluoromethylornithine (DFMO) as target of *MYCN*, and the combination of chemotherapy with the ALK inhibitor Crizotinib for the treatment of high-risk NB patients is currently under testing in clinical trials (Zafar et al. 2021).

Despite the important achievements in improving the outcome of neuroblastoma patients, only one-third of children with high-risk cases are expected to be long-term survivors (Matthay et al. 1999). In fact, cancer cells are able to tolerate DNA damages induced by chemotherapy and radiotherapy and to exploit alternative DNA repairing systems, thus developing resistance to cytotoxic drugs. Therefore, neuroblastoma remains a challenge in pediatric oncology and the need of new therapies designed to target to specific genetic and epigenetic alterations has become imperative to improve the outcome of high-risk NB patients with refractory disease or chemo-resistant relapse. (Ponzoni et al. 2022)

1.2 Genetic basis of neuroblastoma

The contribution of genetic predisposition is particularly important in pediatric cancers. Neuroblastoma tumors, as well as other pediatric cancers, present few recurrent somatic mutations but frequent chromosomic aberrations

(Capasso and Diskin 2010) and about 10% of cases are associated with pathogenic germline mutations in cancer genes (Grobner et al. 2018, Zhang et al. 2015). In the last decades, linkage scans of families with the disease, genome-wide association studies (GWAS) and next generation sequencing have gained a more comprehensive understanding of neuroblastoma heritability (Tonini and Capasso 2020).

1.2.1 Chromosomal copy number alterations and rearrangements

Chromosomal copy number changes are the most common genetic event in neuroblastoma, with *MYCN* amplification, 17q gain, 1p deletion, and 11q deletion as the more frequent (Capasso and Diskin 2010).

The genetic aberration most consistently associated with poor outcome is the genomic amplification of *MYCN*, which occurs in about 20% of primary tumors and it is strongly correlated with advanced stage disease and treatment failure (Brodeur et al. 1984, Schleiermacher et al. 2011). *MYCN* is a master regulator of transcription that can activate hallmark cancer genes and has a well-established and crucial role in promoting tumor growth and progression. Moreover, *MYCN* is to date one of the most important biomarker for neuroblastoma risk stratification (Tonini, Boni, et al. 1997, De Bernardi et al. 2008). Gain of 17q occurs in over half of NB cases (70%) and identifies unfavorable prognosis (Vandesompele et al. 2005). Another frequent finding in neuroblastoma is the loss of tumor suppressor regions, for example chromosome 1p loss of heterozygosity (LOH) which correlates with poor prognosis, or 11q deletion detected in 35%-40% of primary tumors (Takita 2021). Chromosomal rearrangements can involve also the orphan receptor tyrosine kinase *ALK*, normally expressed in the developing embryonic and neonatal central nervous system. *ALK* is the most common somatically mutated gene in neuroblastoma (Mosse et al. 2008) and, since it is located proximal to the *MYCN* locus, it can be co-amplified with *MYCN*, even if solitary *ALK* amplification rarely occurs (Takita 2021). Other copy number variations (CNVs) involved in neuroblastoma

predisposition are deletion at 1q21.1, containing a gene belonging to the NB breakpoint family (*NBPF23*), and a rare microdeletion at 16p11.2, containing causal candidate genes *SEZ6L2* and *PRRT2* associated with NB development (Tonini and Capasso 2020, Egolf et al. 2019). Loss-of-function genetic alterations (somatic mutations, small indels, and single nucleotide variations) of *ATRX*, which encodes chromatin remodeling proteins in the telomeric region, have been detected in approximately 10% of patients with neuroblastoma (Peifer et al. 2015, Valentijn et al. 2015). Moreover, rearrangements of the promoter region of *TERT* encoding the catalytic subunit of telomerase were detected in approximately 25% of neuroblastoma cases (Peifer et al. 2015, Valentijn et al. 2015). The presence of copy number variations (CNVs) in a tumor cell suggests that the genome is instable and can be prone to replication errors or abnormal mitosis. This condition is known as chromosome instability (CIN) and several CIN associated genes have been discovered in the last years (Tonini and Capasso 2020). Numerical CNVs are largely present in localized NB and are associated with a better prognosis, whereas structural CNVs are mainly represented in advanced metastatic tumors (Schleiermacher et al. 2012, Stigliani et al. 2012). The special stage 4S, which includes patients younger than 1 year with metastatic disease, has tumor cells with primarily numerical CNVs, but few structural CNVs (Coco et al. 2012). A lot of evidences suggest that CIN initiates in the early phase of embryonic life just during NCCs migration, probably triggered by the malfunction of the cellular systems dedicated to preserve the genome identity (Tonini and Capasso 2020). Hence, CIN is widely recognized as one of the major player in NB oncogenesis and tumor heterogeneity (Tonini 2017).

1.2.2 Familial neuroblastoma

Familial NB usually occurs at a young age and is more likely than sporadic tumors to present with multiple primary tumor sites (Tonini and Capasso 2020). Familial forms of neuroblastoma represent only 1–2% of cases and are inherited in an autosomal dominant manner (Capasso and Diskin 2010). The first gene

implicated in familial NB tumorigenesis was *PHOX2B* (Trochet et al. 2004, Perri et al. 2005) which encodes a transcription factor driving neural crest differentiation towards noradrenergic neurons (Pattyn et al. 1999) and has already been associated with congenital central hypoventilation syndrome (CCHS) (Serra et al. 2008). *PHOX2B* germline mutations account for ~10% of familial NB (Mosse et al. 2004, Raabe et al. 2008), and have also been observed in up to 2% of sporadic cases (van Limpt et al. 2004, Serra et al. 2008). Recently, an analysis of the NB super-enhancer landscape has demonstrated that *PHOX2B* governs a regulatory circuit that confers a sympathetic noradrenergic identity to tumor (Boeva et al. 2017), whereas functional studies showed that reduced *PHOX2B* dosage, due to heterozygous deletion or dominant-negative mutations, blocks differentiation of sympathetic neuronal precursors generating a cell population more susceptible to secondary transforming events (Reiff et al. 2010, Pei et al. 2013).

The second major susceptibility gene in familial neuroblastoma to be identified was *ALK*, whose gain-of-function mutations account for 75% of familial cases (Schimke, Collins, and Stolle 2010). Germline *ALK* mutations are mainly located in the kinase domain of the encoded tyrosine kinase receptor and show incomplete penetrance. In addition to its role in familial NB, *ALK* represents also the most frequently somatically mutated gene in sporadic NBs (10–12% of primary sporadic NB tumors) (Janoueix-Lerosey et al. 2008, Mosse et al. 2008).

Despite significant advancement in understanding the genetic factors that predispose to familial NB, a non-negligible portion of familial cases, about 15%, remains currently unresolved (Capasso et al. 2020). Beyond *ALK* and *PHOX2B*, no other mutated genes have been associated with familial NB. Mutations in *KIF1Bβ* (Yeh et al. 2008) and *GALNT14* (De Mariano et al. 2015) and alterations in 16p12–13 (Maris et al. 2002), 4p16 (Perri et al. 2002), and 1p loci (Lo Cunsolo et al. 1999, Tonini, Lo Cunsolo, et al. 1997) have been reported in related patients, but further validations are needed.

1.2.3 Sporadic Neuroblastoma

Only a small proportion of sporadic NB cases carry an identifiable somatic oncogenic mutation, suggesting that heritable genetic risk variants have a relevant role in NB carcinogenesis (Pugh et al. 2013, Lasorsa et al. 2016, Esposito et al. 2018). Furthermore, neuroblastoma is a very rare disease, making the study of genetic susceptibility even more challenging. Whole-exome sequencing approaches have allowed the identification of rare genetic variants that are associated with neuroblastoma predisposition in patients who lack the classic clinical criteria for a cancer predisposition syndrome. Candidate gene studies and GWAS were also used to explore the contribution of prevalent genetic variations.

1.2.4 Uncommon moderate-penetrance genetic variants

In recent years, different groups have identified genes enriched in rare pathogenic germline variants in children with NB, which presumably have a larger effect on genetic predisposition compared to common ones (Pugh et al. 2013, Lasorsa et al. 2016, Esposito et al. 2018). Pathogenic and likely pathogenic variants were identified in predisposition genes such as *ALK*, *AXIN2*, *CHEK2*, *PINK1*, *TP53*, *PALB2*, and *BARD1* (Pugh et al. 2013, Lasorsa et al. 2016, Capasso et al. 2020) but also in candidate genes like *APC*, *BRCA1*, *BRCA2*, *LZTR1*, *SDHB* and *SMARCA4* (Parsons et al. 2016, Zhang et al. 2015, Grobner et al. 2018). Specifically, *TP53* variants discovered by a large GWAS study on three independent case-control cohorts, very strongly associated with NB predisposition (Diskin et al. 2014). It is interesting to note that most of the rare germline variants reported involve genes crucial for DNA repair and maintenance of genomic integrity.

Other rare risk variants are those associated with syndromic diseases in which is observed recurrence of NB onset, such as *NF1* in neurofibromatosis type 1 (Origone et al. 2003), *PTPN11* in Noonan syndrome (Mutesa et al. 2008),

HRAS in Costello syndrome (Kratz et al. 2011), *TP53* in Li Fraumeni syndrome (Birch et al. 2001), *EZH2* in Weaver syndrome (Tatton-Brown et al. 2013), *SDHB* in familial paraganglioma/pheochromocytoma (Schimke, Collins, and Stolle 2010), *CDKN1C* in Beckwith-Wiedemann syndrome (Maas et al. 2016), and *MSX1* in Wolf- Hirschhorn Syndrome (Ozcan et al. 2017). However, the complete spectrum of rare germline variants predisposing to NB remains to be defined.

1.2.5 Common low-penetrance genetic variants

Genome-wide association studies (GWAS) shed light on the genetic complexity of neuroblastoma, disclosing common polymorphic alleles that can influence tumor development and progression. Many highly significant polymorphic alleles have been identified that can influence neuroblastoma development (Bosse and Maris 2016) and although each association has a modest individual effect on disease initiation, multiple alterations can cooperate to promote malignant transformation during neurodevelopment.

Many GWAS-defined neuroblastoma susceptibility loci and genes have been identified including *CASC15* (Maris et al. 2008), *BARD1* (Capasso et al. 2009), *LMO1* (Wang et al. 2011), *HACE1*, and *LIN28B* (Diskin et al. 2012) associated with high-risk NB, whereas *DUSP12*, *HSD17B12*, *DDX4*, and *IL31RA* associated with the low-risk NB group (**Fig. 1.3**) (Nguyen le et al. 2011, Capasso et al. 2013).

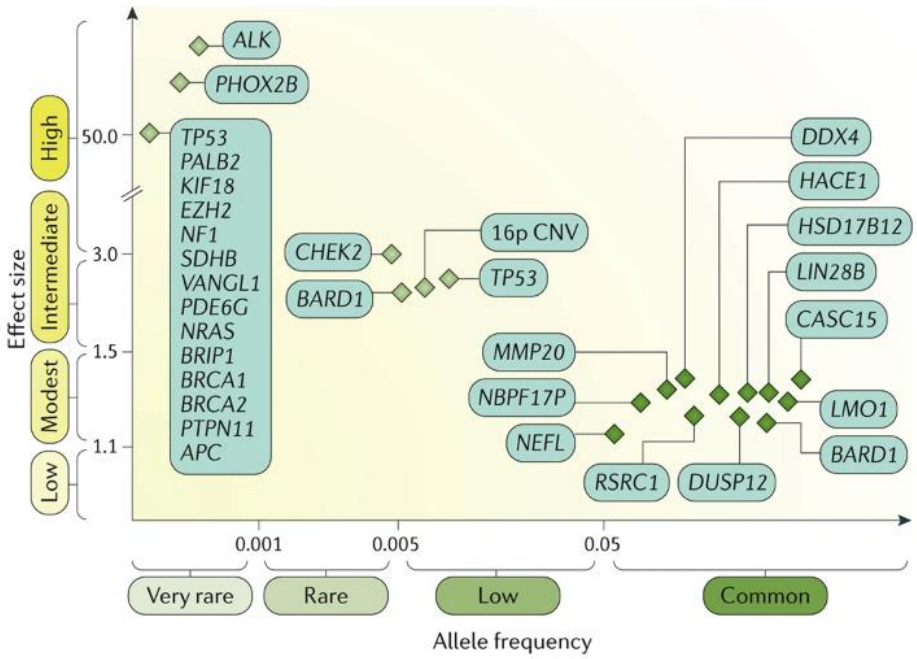


Figure 1.3 Genetic predisposition to neuroblastoma. *ALK* and *PHOX2B* mutant alleles are very rare in the population, are inherited in an autosomal dominant Mendelian manner and cause familial neuroblastoma with high penetrance. Other genes with germline damaging mutations that can predispose to neuroblastoma have been identified (such as *TP53*, *NRAS* and *BRCA2*), but the clinical relevance of many of these mutations remains to be determined. Several common polymorphisms (such as *BARD1* or *LMO1*) with small individual effect on tumor, can cooperate to lead to sporadic neuroblastoma tumorigenesis. Hundreds of others alleles are predicted to exist, which might explain the heritability of neuroblastoma. CNV, copy number variant. *Adapted from Matthay et al. Neuroblastoma. Nat Rev Dis Primers 2, 16078 (2016).*

The first GWAS on NB identified a susceptibility locus at chromosome 6p22 in a newly identified long noncoding RNA (lncRNA) annotated as *CASC15* gene. (Maris et al. 2008, Russell et al. 2015). A SNP in *CASC15* produces a truncated isoform *CASC15-S*, whose reduced expression has been correlated with the more aggressive high-risk NB subset (Russell et al. 2015). Loss of another lncRNA, *NBAT-1* (*CASC14*), also found at the 6p22 susceptibility locus, causes proliferation and invasion (Pandey et al. 2014). Moreover, *CACSC15* and *NBAT1* are particularly interesting since in normal conditions they favor the differentiation of neuronal precursors through their regulatory interactions with

important cancer-associated *SOX9* and *USP36* genes located on chromosome 17q, a region often gained in high-risk NB (Mondal et al. 2018).

A second GWAS analysis restricted to high-risk patients found different predisposing SNPs in *BARD1* at chromosome 2q35 (Capasso et al. 2009). Diverse functional studies have elucidated the role of *BARD1* and its variants in NB development (Cimmino, Formicola, and Capasso 2017). A genetic variant in the *BARD1* promoter decreases the expression of the full-length form of *BARD1*, which has oncosuppressor functions and protects NB cells from DNA damage (Cimmino et al. 2018, Cimmino et al. 2020), whereas variants in introns increase the expression of the oncogenic isoform *BARD1β*, (Bosse et al. 2012) which can induce cell growth and stabilizes the Aurora kinases (Ryser et al. 2009, Bosse et al. 2012).

A third NB risk locus was identified at chromosome 11p15.4 close to *LMO1* by using an expanded GWAS (Wang et al. 2011). *LMO1* decreased expression, caused by a variant in a super-enhancer element that ablated a canonical GATA transcription factor binding site (Wang et al. 2011), was associated with increased risk of aggressive NB forms (Wang et al. 2011, Zhu et al. 2017). Two additional new genome-wide significant independent signals were identified at chromosome 6q16 within the genes *LIN28B* and *HACE1* (Diskin et al. 2012). Functional investigations at this locus showed that the activation of *LIN28B* due to genetic variants, enhances *MYCN* levels via let-7 microRNA suppression (Diskin et al. 2012, Molenaar et al. 2012, Powers et al. 2016) and have explained how *LIN28B* promotes malignant transformation in NB (Powers et al. 2016, Schnepp et al. 2015, Molenaar et al. 2012, Corallo et al. 2020).

The genetic landscape of sporadic NB has been amplified with the discovery of additional susceptibility variants at *RSRC1*/*MLF1* (3q25) and *CPZ* (4p16) (McDaniel et al. 2017), *HSD17B12* (11p11.2) (Capasso et al. 2013, Nguyen le et al. 2011, Zhang et al. 2017), *DUSP12* (1q23.3) (Capasso et al. 2013, Nguyen le et al. 2011), *SPAG16* (2q34) (Gamazon et al. 2013), *NEFL* (8p21.2)

(Capasso et al. 2014), and *CDK1NB* (12p13.1) (Capasso et al. 2017). In-depth functional analyses of these loci are needed to define the biological role of the found variants and the associated genes in the development of NB.

Genome-wide approaches have been also used to demonstrate interactions between germline disease predisposing variants and somatically acquired genomic aberrations, or to investigate other aspects relevant to the disease management. Indeed, SNPs in *MMP20* (Chang et al. 2017) and *KIF15* (Hungate et al. 2017) have been associated with NB susceptibility only in association with 11q deletion and *MYCN* amplification respectively, whereas another study showed that specific mtDNA haplogroups can influence the risk of NB (Chang et al. 2020). Instead, SNPs in *PARP1* and *IL6* seemed to be predictive biomarkers of response to chemotherapy and prognosis (Totaro et al. 2013, Avitabile, Lasorsa, et al. 2020).

Finally, our recent works focused on another interesting aspect related to NB genetics. We provided evidence that common genetic architecture can lead to inter-individual susceptibility to diverse pathological conditions and in particular that some risk loci can be shared between NB and other complex diseases and tumors. We demonstrated that risk SNPs in 2q35, 3q25.32, and 4p16.2 were cross-associated with NB and congenital heart diseases (CHD) that, similar to NB, originate from abnormal neural crests formation (Testori et al. 2019). Interestingly, some of these shared susceptibility loci regulate the expression of relevant genes involved in neural crest cells formation and developmental processes, such as *BARD1*, *MSX1*, and *SHOX2* (Testori et al. 2019). Moreover, we found a genome-wide signal at locus 1p13.2 correlated with decreased *SLC16A1* expression, which showed cross-association with NB and melanoma (Avitabile, Succoio, et al. 2020), demonstrating for the first time that neural crest derived tumors share disease predisposing variants.

All of the above described studies have not only identified genetic risk loci for NB but have unraveled novel biological processes underlying this challenging disease. Additionally, these findings can have implications in the

development of new therapeutic strategies, thus highlighting the importance of performing GWAS studies and functional post-GWAS functional investigations.

1.3 Genome Wide Association Studies (GWAS) and post-GWAS studies

Over the last 10 years, the use of Genome Wide Association Studies (GWAS) has allowed us to elucidate the genetic basis of predisposition to neuroblastoma. GWAS is a high-throughput approach to genotype hundreds of thousands of SNPs to identify across the entire human genome associations between common single nucleotide polymorphisms (SNPs) and disease risk. The GWAS method is thus particularly suitable to understand polygenic diseases where multiple gene variants, each with a potentially small effect, act together to induce the disease (Studies et al. 2007). Indeed, although each association may have a modest individual effect on disease initiation, multiple alterations can cooperate to promote malignant transformation.

The theoretical basis of GWAS is linkage disequilibrium (LD), since it is possible to assume that there is a strong LD between the lead SNP of a risk locus, that is the one mainly responsible for the genetic association with the interested disease, and the true causal variant (Hinds et al. 2005).

The study design of a typical GWAS expects to genotype 1 million or more SNPs in the entire human genome in a case-control setting. Then, differences in allele frequency between cases and controls at each marker locus are evaluated for all genetic markers (**Fig. 1.4**) (Hinds et al. 2005). To determine whether a SNP locus is associated with a disease, its allelic frequency should be significantly different between the case and the control groups.

Respect to single gene approaches, GWAS have greater statistical power to detect variant with even small or modest effect sizes. Moreover, since genomic technology has advanced and costs have decreased, GWAS have become a popular and efficient way to study common genetic traits. Despite that, one possible limitation to account for is that most of the found gene variations are common mutations, mainly occurring in intron and intergenic regions, so

they are loci that do not seem to correlate with disease/ trait examined. GWAS meta-analysis may be a good solution to improve the power of these studies and to investigate the consistency or heterogeneity of these associations across diverse datasets and study populations (Oei et al. 2014).

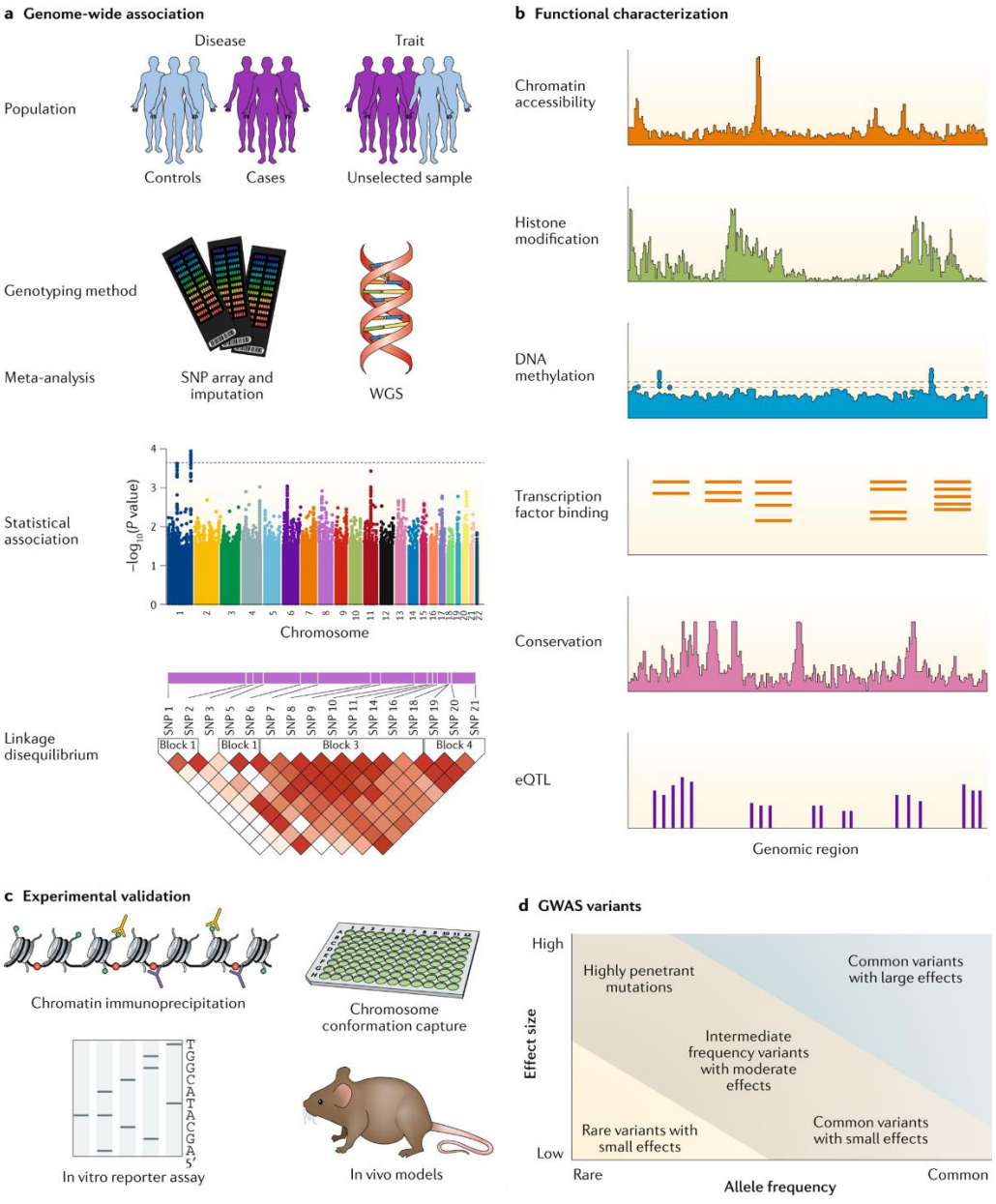


Figure 1.4 GWAS study design. A) The aim of a genome-wide association study (GWAS) is to detect associations between allele or genotype frequency and a disease or a trait. Every GWAS starts from the selection of an appropriate study population depending on the trait or disease to investigate (for example, cases and controls for a

disease, or an unselected population sample for a trait). The following step is the Genotyping, which can be performed using single-nucleotide polymorphism (SNP) arrays combined with imputation or whole-genome sequencing (WGS). Association tests are used to identify regions of the genome associated with the phenotype of interest at genome-wide significance. Usually, causal variants are not among the SNPs directly genotyped but are in linkage disequilibrium with them. Meta-analysis can be performed to increase the statistical power of the detected associations. **B)** Functional characterization of genetic variants is often required to move from statistical association to causal variants and genes, especially in the non-coding genome. Computational methods are used to predict the regulatory effect of non-coding variants on the basis of functional annotations. **C)** Target genes can be identified or confirmed using *in vitro* assays, and experimentally validated using cell-based systems and model organisms. **D)** A representation of the spectrum of the genetic variants allele frequencies and effect sizes. eQTL, expression quantitative trait locus. *Adapted from Tam et al., Nat Rev Genet 20, 467–484 (2019).*

GWAS have been successful in uncovering thousands of genetic variants that influence risk for complex human traits and diseases, and a notable number of these loci are well-replicated, suggesting that they are true associations (Welter et al. 2014, Gallagher and Chen-Plotkin 2018). However, several elements have made it difficult to bridge the gap between the statistical associations that link locus and trait, and a functional understanding of the biology underlying disease risk (Gallagher and Chen-Plotkin 2018). For example, the association of a locus with a trait does not specify which variant is actually the causal one or which gene could be the causal variant target. Moreover, the majority of disease-associated variants are located in non-coding genomic regions or are far away from the nearest known gene (Schaub et al. 2012, Maurano et al. 2012). Overall, while several thousand GWASs have been performed and many thousands of loci have been confirmed as disease risk factors, the number of studies that have functionally characterized candidate causal variants at a given locus is still low. Moreover, functional investigation aims at identify the molecular functions of the causal variants, which genes are affected by the causal variants and how changes in the regulation of the causal genes lead to altered disease risk. For this reason, post-GWAS characterization of already-identified GWAS loci, rather

than a search for ever more GWAS loci, seems to be most likely to benefit knowledge of pathophysiology.

1.4 ***HSD17B12,*** Hydroxysteroid 17-Beta Dehydrogenase 12

17β-Hydroxysteroid dehydrogenases (HSD17B) are a class of enzymes known for their role in oxidation or reduction in position C17 of 17β-hydroxy or 17β-keto groups respectively, in C18 and C19 steroids (Hiltunen et al. 2019). In mammals, HSD17Bs are represented by at least 14 different enzymes with amino acid sequence similarities, all displaying catalytic activities towards 17β steroid substrates, but with different non-steroid activities, depending on tissue specificity and subcellular localizations, towards substrates including retinols, cholesterol, secondary alcohols, xenobiotics and thioesters of various long-chain carboxylic acids including fatty acids and their metabolites (Moeller and Adamski 2006, Hiltunen et al. 2019).

HSD17B12, located at 11p11.2, encodes for a multifunctional isozyme involved in estrone to estradiol conversion (Kemilainen et al. 2016) but also in the elongation of long chain fatty acids (LCFA), particularly in the production of arachidonic acid from the conversion of palmitate (Luu-The, Tremblay, and Labrie 2006). Notably, Arachidonic acid is the precursor of prostaglandin E2, an important mediator of inflammation, linking *HSD17B12* expression levels to inflammation and cancer (Harizi, Corcuff, and Gualde 2008, Hou, Yu, and Jiang 2022).

The fatty acids elongation pathway is a biological process that takes place at the endoplasmic reticulum membranes and involves multiple enzymes that act together as one physiological functional unit to produce Long-chain fatty acids (LCFAs), containing more than 18 carbon atoms, and Very long-chain fatty acids (VLCFAs), containing more than 22 carbons atoms (Mohamed et al. 2020, Sassa and Kihara 2014, Kihara 2012). Fatty acids elongation occurs through a cycling process made of four steps, respectively condensation, reduction, dehydration and reduction, the second of which is catalyzed by HSD17B12 (**Fig. 1.5**). The

first rate-limiting step is performed by the elongases ELOVL1-7, which exhibit characteristic substrate specificity. HSD17B12, in the second step, catalyzes in an NADPH-dependent manner the reduction of 3-ketoacyl-CoA in 3-hydroxyacyl-CoA, and together with dehydratases (HACD1-4), reductase (TER) and desaturases (FADS1-2) contribute to the generation of a variety of LCFAs and VLCFAs differing in chain-length and number of double bonds (Sassa and Kihara 2014, Kihara 2012). Saturated and monounsaturated LCFAs derive from elongation of palmitic acid, whereas polyunsaturated fatty acids (PUFAs) originate from two essential FAs, the linoleic acid (LA, C18:2) and α-linolenic acid (ALA, C18:3) that generate the ω-6 and ω-3 FA series, respectively (Tsachaki et al. 2020, Saini and Keum 2018).

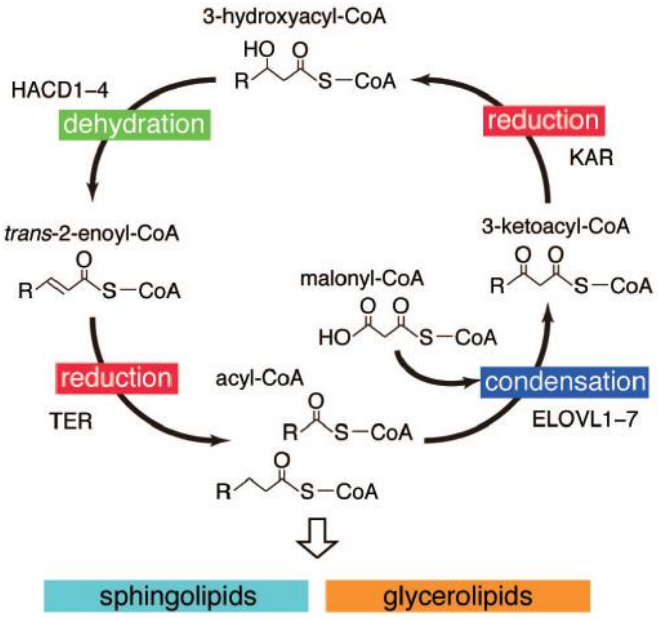


Figure 1.5 Mammalian fatty acids elongation cycle. The fatty acids elongation cycle consists of four enzymatic reactions that take place at the Endoplasmic Reticulum surface. In each cycle, acyl-CoA incorporates two carbon units from malonyl-CoA. The enzymes involved in each step are illustrated. *Adapted from J. Biochem. 2012;152(5):387–395*

Mammals display a variety of distinct FAs with unique molecular properties and cellular functions, for example in skin barrier formation, liver

homeostasis, myelin maintenance, spermatogenesis, and anti-inflammation (Kihara 2012, Tsachaki et al. 2020).

Analysis of the *HSD17B12* mRNA level in mammalian tissues shows that *HSD17B12* gene is widely expressed (Saloniemi et al. 2012) and according to the Human Protein Atlas database (https://www.proteinatlas.org/) the highest HSD17B12 protein level is found in kidney and in tissues involved in lipid metabolism, including liver and muscle (Sakurai et al. 2006), but lower protein levels are present in various mammalian tissues.

An elaborate transcriptomic study of 17 different cancer types in a total of around 8000 patients was performed using data of the Cancer Genome Atlas and the Human Protein Atlas Projects, and showed that *HSD17B12* correlates with either good or poor prognosis depending on the tumor type (Uhlen et al. 2017). For example, *HSD17B12* emerged as a favorable prognostic gene in renal cancer but unfavorable factor in liver cancer, or it showed different oncogenic or oncosuppressor roles in different breast cancer cell lines (Uhlen et al. 2017, Tsachaki et al. 2020). siRNA-mediated knockdown of *HSD17B12* expression in cultured breast cancer cells resulted in inhibition of cell proliferation and migration, biological effects that have been linked to *HSD17B12* participation in metabolism of arachidonic acid (Nagasaki et al. 2009, Tsachaki et al. 2020). *HSD17B12* expression was significantly higher in breast tumor tissues than in normal tissues, leading to an increased risk of recurrence and adverse clinical outcome (Song et al. 2006, Nagasaki et al. 2009). Similarly, *HSD17B12* weak expression correlated with a better overall survival in ovarian cancer patients (Szajnik et al. 2012), and immune-histochemical analyses indicated that *HSD17B12* cytoplasmic staining was enhanced along with the severity of ovarian cancer, mimicking *COX-2* expression and leading to increased prostaglandin production during ovarian cancer progression (Kemilainen et al. 2018). In squamous cell carcinoma of the head and neck (SCCHN), elevated expression of *HSD17B12* mRNA is predictive of metastasis (Rickman et al. 2008). Moreover, *HSD17B12* expression levels have been associated with

adipocyte differentiation as well as embryogenesis and differentiation in mice (Bellemare et al. 2009, Rantakari et al. 2010). Mice lacking *HSD17B12* (*HSD17B12* KO) showed early embryonic lethality and reduced-size embryos with severely disrupted organogenesis (Rantakari et al. 2010, Bellemare, Phaneuf, and Luu-The 2010). Finally, *HSD17B12* involvement in inflammatory processes is strongly supported by the numerous reports from the literature that link the activity of this gene to the production of Prostaglandin E2 (PGE2), a potent inflammatory mediator that cancer cells produce and release into the extracellular environment to suppress infiltrating immune cells (Tsachaki et al. 2020, Song et al. 2009, McNerney et al. 2020). Indeed, it has been extensively demonstrated that Prostaglandin E2 promotes tumor cell proliferation, migration , and invasion, boosting an inflammation-enriched microenvironment directed toward evasion from the immune system (Wang and Dubois 2010, Hu, Fromel, and Fleming 2018, Hou et al. 2022).

1.5 Lipid metabolism in neuroblastoma and related therapeutic strategies

Metabolic reprogramming is considered a hallmark of malignant tumors, since it confers cancer cells the ability to survive, proliferate and metastasize (Li and Zhang 2016, Koundouros and Poulogiannis 2020, Bansal, Gupta, and Ding 2022, Tao et al. 2022). Cancer cells own the ability to rewire their lipid metabolism to sustain the production of metabolic substrates for energy storage, membrane-building components, and signaling transduction molecules, which have been shown to be strongly associated with cancer prognosis (Rohrig and Schulze 2016, Agostini et al. 2022).

Neuroblastoma and especially high-risk NB cases are among the tumors in which lipid metabolic reprogramming covers a central role in cancer initiation and progression. In fact, positron emission tomography of cancer patients shows that NB tumors have high glucose uptake and a high rate of lactic acid production, indicating that these tumors rely on oxidative phosphorylation rather than glycolysis for the production of energy (Agostini et al. 2022). Moreover,

reprogramming of lipid metabolism in cancer cells includes changes in fatty acid transport, *de novo* fatty acid synthesis, storage as lipid droplets, and fatty acid -oxidation to generate Acetyl-CoA for driving the TCA cycle and ATP production (**Fig. 1.6**) (Rohrig and Schulze 2016, Carracedo, Cantley, and Pandolfi 2013, Bansal, Gupta, and Ding 2022).

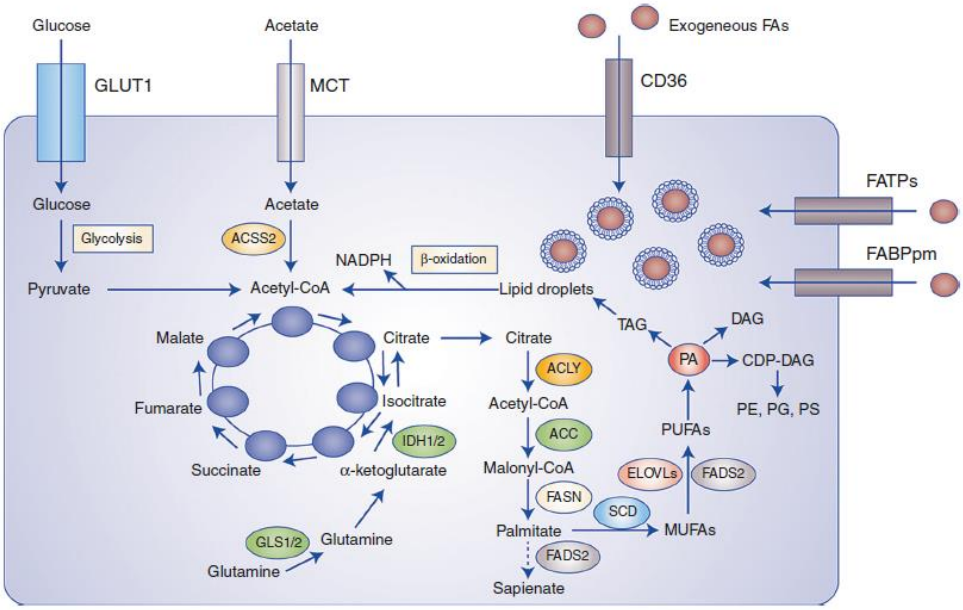


Figure 1.6 Schematic representation of cellular lipid metabolism. Cancer cells can obtain fatty acids (FAs) from *de novo* lipogenesis or from the exogenous uptake. The exogenous uptake of FAs from the surrounding microenvironment is facilitated by specialized transporters, including *CD36*, *FATPs* and *FABPpm*. FAs and their derivatives can be stored in lipid droplets, and used for energy production through β-oxidation. Cancer cells rely on glucose, glutamine and acetate to synthesize citrate, which is ultimately used to generate Palmitate through the enzymatic activities of *ACLY*, *ACC* and *FASN*, and can subsequently be de-saturated and elongated to form a diverse group of lipid species. An alternative pathway for palmitate desaturation exists, which generates sapienate through *FADS2*, instead of palmitoleate. Abbreviations: *GLUT1*, glucose transporter 1; *MCT*, monocarboxylate transporter; *CD36*, cluster of differentiation 36; *FATPs*, fatty acid transport proteins; *FABPpm*, fatty acid-binding protein; *GLS*, glutaminase; *IDH1/2*, isocitrate dehydrogenase; *ACLY*, ATP–citrate lyase; *ACSS2*, acyl-CoA synthetase short-chain family member 2; *ACC*, acetyl-CoA carboxylase; *FASN*, fatty acid synthase; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; *SCD*, stearoyl-CoA desaturase-1; *FADS*2, fatty acid desaturase 2; *ELOVLs*, elongation of very long-chain fatty acid protein; PA, phosphatidic acid; TAG, triacylglycerol; DAG, diacylglycerol; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PS; phosphatidylserine.

Adapted from British Journal of Cancer (2020) 122:4–22

An important aspect that must be considered when discussing general and lipid metabolic alterations in neuroblastoma is the amplification of *MYCN*, which is the most robust clinical biomarker of the poor clinical outcome in NB and is present in about 40% of high-risk cases (Brodeur et al. 1984). It has been shown that *MYCN* is able to promote glycolysis (Oliynyk et al. 2019), lipogenesis (Ruiz-Perez et al. 2021, Moreno-Smith et al. 2021) and metabolism of glutamine (Oliynyk et al. 2019, Ren et al. 2015), serine (Xia et al. 2019), and polyamine (Gamble et al. 2019) to enhance macromolecular biosynthesis and energy production. Indeed, *MYCN* amplification enhances oxidative phosphorylation in NB cells and it is associated with elevated expression of key enzymes involved in glycolysis, Krebs cycle, and electron transport chain proteins. These genes have been linked to patients' poor overall survival (Oliynyk et al. 2019). Moreover, inhibition of *MYCN* and its downstream signaling pathway results in intracellular lipid droplet accumulation in NB cells as a consequence of mitochondrial dysfunction (Zirath et al. 2013).

To date, inhibition of lipid metabolism has been explored as a novel therapeutic strategy to improve clinical outcome of neuroblastoma treatment (Agostini et al. 2022). Some of the strategies most used up to now and which are giving promising results are the inhibitions of fatty acids oxidation and of *de novo* fatty acid synthesis. A recent approach used in preclinical studies and aimed at targeting β-oxidation, is the treatment with Etomoxir, a small-molecule that works as irreversible inhibitor of Carnitine palmitoyl-transferase 1a (*CPT1a*). *CPT1a* is the β-oxidation rate-limiting enzyme and its high expression correlates with poor prognosis in NB patients (Oliynyk et al. 2019). Etomoxir treatment was able to reduce *in vivo* tumor growth of *MYCN*-amplified NB cells, but in phase II clinical trials showed hepatic toxicity and was suspended (Oliynyk et al. 2019). Notably, Ruiz-Pérez et al. demonstrated that the inhibition of *de novo* fatty acids synthesis was able to reduce neuroblastoma growth *in vitro* and *in vivo*, and to induce neural differentiation through *ERK* activation (Ruiz-

Perez et al. 2021). In this work, the authors tested five available small-molecule inhibitors of key enzymes in fatty acid synthesis. In detail, they used TOFA and Soraphen A, which target Acetyl- CoA carboxylase (*ACACA*), and Cerulenin, Orlistat, and UB006 that target fatty acid synthase (*FASN*) (Ruiz-Perez et al. 2021). Of note, the observed antitumor effects were independent from *MYCN* status. A further lipid pathway which is gaining more and more attention and which is also closely connected to *HSD17B12* is the production of eicosanoids, and in particular of Prostaglandin E2. Prostaglandin E2 is a well-known inflammatory player which promotes tumor cell proliferation, migration and invasion (Wang and Dubois 2010, Hu, Fromel, and Fleming 2018, Hou et al. 2022). Very recently, Hou and colleagues provided proof-of-concept evidence that prostaglandin receptor PGE2 (*PTGER2*) represent a promising anti-inflammatory target for the treatment of NB with various high-risk factors including 11q deletion and *MYCN* amplification (Hou et al. 2022).

2. AIMS

Over the last decades, the analysis of the neuroblastoma genetic landscape led to important clinical progresses. Disease-linked SNPs found by GWAS often represent regulatory elements with a small effect on fitness and viability, but a relatively large effect on the analyzed disease. Thus, the investigation of neuroblastoma-associated SNPs may provide new and interesting insights that will enrich our current knowledge about the genetic and biological landscape of this complex cancer.

The aim of this project is to functionally characterize the 11p11.2 neuroblastoma predisposition locus, to identify new molecular regulatory mechanisms underlying neuroblastoma tumorigenesis. In addition, we aim to identify novel causative biological pathways, which may in the future yield opportunities to discover new therapeutic agents or targets and to identify biomarkers to monitor disease progression or treatment response. Moreover, the results obtained in the present study could be included in the calculation of Polygenic Risk Scores, which help to understand how combinations of variants work together, ultimately allowing to better define the risk of developing neuroblastoma. Deepening the knowledge regarding neuroblastoma genetic predisposition through functional characterization studies could also permit to improve or anticipate patients' diagnosis, and to better stratify patients into risk groups.

7. ACKNOWLEDGEMENTS

This study was supported by grants from Fondazione Italiana per la Lotta al Neuroblastoma, (GENEDREN project) to M. Capasso, from OPEN Associazione Oncologia Pediatrica e Neuroblastoma ONLUS to M. Capasso and from Associazione Italiana per la Ricerca sul Cancro grant no. 25796 to M. Capasso.

8. LIST OF PUBLICATIONS

1) Schiavi A, Runci A, **Maiorino T**, Naso FD, Barenys M, Fritsche E, Strappazzon F, Ventura N. *Cobalt chloride has beneficial effects across species through a hormetic mechanism*. Front Cell Dev Biol. 2022 Oct 25;10:986835.
2) Avitabile M, Bonfiglio F, Aievola V, Cantalupo S, **Maiorino T**, Lasorsa VA, Domenicotti C, Marengo B, Zbyněk H, Vojtěch A, Iolascon A, Capasso M. *Single-cell transcriptomics of neuroblastoma identifies chemoresistance-associated genes and pathways*. Comput Struct Biotechnol J. 2022 Aug 18;20:4437-4445.
3) Cimmino F, Montella A, Tirelli M, Avitabile M, Lasorsa VA, Visconte F, Cantalupo S, **Maiorino T**, De Angelis B, Morini M, Castellano A, Locatelli F, Capasso M, Iolascon A. *FGFR1 is a potential therapeutic target in neuroblastoma.* Cancer Cell Int. 2022 Apr 29;22(1):174.
4) Di Rita A, Angelini DF, **Maiorino T**, Caputo V, Cascella R, Kumar M, Tiberti M, Lambrughi M, Wesch N, Löhr F, Dötsch V, Carinci M, D'Acunzo P, Chiurchiù V, Papaleo E, Rogov VV, Giardina E, Battistini L, Strappazzon F. *Characterization of a natural variant of human NDP52 and its functional consequences on mitophagy*. Cell Death Differ. 2021 Aug;28(8):2499-2516.
5) Capasso M, Montella A, Tirelli M, **Maiorino T**, Cantalupo S, Iolascon A. *Genetic Predisposition to Solid Pediatric Cancers*. Front Oncol. 2020 Oct 28;10:590033.
6) Di Rita A, **Maiorino T**, Bruqi K, Volpicelli F, Bellenchi GC, Strappazzon *F. miR-218 Inhibits Mitochondrial Clearance by Targeting PRKN E3 Ubiquitin Ligase*. Int J Mol Sci. 2020 Jan 5;21(1):355.

9. REFERENCES

Agostini, M., G. Melino, B. Habeb, J. M. Calandria, and N. G. Bazan. 2022. "Targeting lipid metabolism in cancer: neuroblastoma." *Cancer Metastasis Rev* no. 41 (2):255-260. doi: 10.1007/s10555-022-10040-8.

Angstman, K. B., J. S. Miser, and W. B. Franz, 3rd. 1990. "Neuroblastoma." *Am Fam Physician* no. 41 (1):238-44.

Antunes, P., A. Cruz, J. Barbosa, V. D. B. Bonifacio, and S. N. Pinto. 2022. "Lipid Droplets in Cancer: From Composition and Role to Imaging and Therapeutics." *Molecules* no. 27 (3). doi: 10.3390/molecules27030991.

Audet-Walsh, E., J. Bellemare, L. Lacombe, Y. Fradet, V. Fradet, P. Douville, C. Guillemette, and E. Levesque. 2012. "The impact of germline genetic variations in hydroxysteroid (17-beta) dehydrogenases on prostate cancer outcomes after prostatectomy." *Eur Urol* no. 62 (1):88-96. doi: 10.1016/j.eururo.2011.12.021.

Avitabile, M., V. A. Lasorsa, S. Cantalupo, A. Cardinale, F. Cimmino, A. Montella, D. Capasso, R. Haupt, L. Amoroso, A. Garaventa, A. Quattrone, M. V. Corrias, A. Iolascon, and M. Capasso. 2020. "Association of PARP1 polymorphisms with response to chemotherapy in patients with high-risk neuroblastoma." *J Cell Mol Med* no. 24 (7):4072-4081. doi: 10.1111/jcmm.15058.

Avitabile, M., M. Succoio, A. Testori, A. Cardinale, Z. Vaksman, V. A. Lasorsa, S. Cantalupo, M. Esposito, F. Cimmino, A. Montella, D. Formicola, J. Koster, V. Andreotti, P. Ghiorzo, M. F. Romano, S. Staibano, M. Scalvenzi, F. Ayala, H. Hakonarson, M. V. Corrias, M. Devoto, M. H. Law, M. M. Iles, K. Brown, S. Diskin, N. Zambrano, A. Iolascon, and M. Capasso. 2020. "Neural crest-derived tumor neuroblastoma and melanoma share 1p13.2 as susceptibility locus that shows a long-range interaction with the SLC16A1 gene." *Carcinogenesis* no. 41 (3):284-295. doi: 10.1093/carcin/bgz153.

Aygun, N. 2018. "Biological and Genetic Features of Neuroblastoma and Their Clinical Importance." *Curr Pediatr Rev* no. 14 (2):73-90. doi: 10.2174/1573396314666180129101627.

Bansal, M., A. Gupta, and H. F. Ding. 2022. "MYCN and Metabolic Reprogramming in Neuroblastoma." *Cancers (Basel)* no. 14 (17). doi: 10.3390/cancers14174113.

Bellemare, V., P. Laberge, S. Noel, A. Tchernof, and V. Luu-The. 2009. "Differential estrogenic 17beta-hydroxysteroid dehydrogenase activity and type 12 17beta-hydroxysteroid dehydrogenase expression levels in preadipocytes and differentiated adipocytes." *J Steroid Biochem Mol Biol* no. 114 (3-5):129-34. doi: 10.1016/j.jsbmb.2009.01.002.

Bellemare, V., D. Phaneuf, and V. Luu-The. 2010. "Target deletion of the bifunctional type 12 17beta-hydroxysteroid dehydrogenase in mice results in reduction of androgen and estrogen levels in heterozygotes and embryonic lethality in homozygotes." *Horm Mol Biol Clin Investig* no. 2 (3):311-8. doi: 10.1515/HMBCI.2010.036.

Birch, J. M., R. D. Alston, R. J. McNally, D. G. Evans, A. M. Kelsey, M. Harris, O. B. Eden, and J. M. Varley. 2001. "Relative frequency and morphology of cancers

in carriers of germline TP53 mutations." *Oncogene* no. 20 (34):4621-8. doi: 10.1038/sj.onc.1204621.

Boeva, V., C. Louis-Brennetot, A. Peltier, S. Durand, C. Pierre-Eugene, V. Raynal, H. C. Etchevers, S. Thomas, A. Lermine, E. Daudigeos-Dubus, B. Geoerger, M. F. Orth, T. G. P. Grunewald, E. Diaz, B. Ducos, D. Surdez, A. M. Carcaboso, I. Medvedeva, T. Deller, V. Combaret, E. Lapouble, G. Pierron, S. Grossetete-Lalami, S. Baulande, G. Schleiermacher, E. Barillot, H. Rohrer, O. Delattre, and I. Janoueix-Lerosey. 2017. "Heterogeneity of neuroblastoma cell identity defined by transcriptional circuitries." *Nat Genet* no. 49 (9):1408-1413. doi: 10.1038/ng.3921.

Bosse, K. R., S. J. Diskin, K. A. Cole, A. C. Wood, R. W. Schnepp, G. Norris, B. Nguyen le, J. Jagannathan, M. Laquaglia, C. Winter, M. Diamond, C. Hou, E. F. Attiyeh, Y. P. Mosse, V. Pineros, E. Dizin, Y. Zhang, S. Asgharzadeh, R. C. Seeger, M. Capasso, B. R. Pawel, M. Devoto, H. Hakonarson, E. F. Rappaport, I. Irminger-Finger, and J. M. Maris. 2012. "Common variation at BARD1 results in the expression of an oncogenic isoform that influences neuroblastoma susceptibility and oncogenicity." *Cancer Res* no. 72 (8):2068-78. doi: 10.1158/0008-5472.CAN-11-3703.

Bosse, K. R., and J. M. Maris. 2016. "Advances in the translational genomics of neuroblastoma: From improving risk stratification and revealing novel biology to identifying actionable genomic alterations." *Cancer* no. 122 (1):20-33. doi: 10.1002/cncr.29706.

Brodeur, G. M., F. A. Hayes, A. A. Green, J. T. Casper, J. Wasson, S. Wallach, and R. C. Seeger. 1987. "Consistent N-myc copy number in simultaneous or consecutive neuroblastoma samples from sixty individual patients." *Cancer Res* no. 47 (16):4248-53.

Brodeur, G. M., and R. C. Seeger. 1986. "Gene amplification in human neuroblastomas: basic mechanisms and clinical implications." *Cancer Genet Cytogenet* no. 19 (1-2):101-11. doi: 10.1016/0165-4608(86)90377-8.

Brodeur, G. M., R. C. Seeger, M. Schwab, H. E. Varmus, and J. M. Bishop. 1984. "Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage." *Science* no. 224 (4653):1121-4. doi: 10.1126/science.6719137.

Capasso, M., M. Devoto, C. Hou, S. Asgharzadeh, J. T. Glessner, E. F. Attiyeh, Y. P. Mosse, C. Kim, S. J. Diskin, K. A. Cole, K. Bosse, M. Diamond, M. Laudenslager, C. Winter, J. P. Bradfield, R. H. Scott, J. Jagannathan, M. Garris, C. McConville, W. B. London, R. C. Seeger, S. F. Grant, H. Li, N. Rahman, E. Rappaport, H. Hakonarson, and J. M. Maris. 2009. "Common variations in BARD1 influence susceptibility to high-risk neuroblastoma." *Nat Genet* no. 41 (6):718-23. doi: 10.1038/ng.374.

Capasso, M., S. Diskin, F. Cimmino, G. Acierno, F. Totaro, G. Petrosino, L. Pezone, M. Diamond, L. McDaniel, H. Hakonarson, A. Iolascon, M. Devoto, and J. M. Maris. 2014. "Common genetic variants in NEFL influence gene expression and neuroblastoma risk." *Cancer Res* no. 74 (23):6913-24. doi: 10.1158/0008-5472.CAN-14-0431.

Capasso, M., and S. J. Diskin. 2010. "Genetics and genomics of neuroblastoma." *Cancer Treat Res* no. 155:65-84. doi: 10.1007/978-1-4419-6033-7_4.

Capasso, M., S. J. Diskin, F. Totaro, L. Longo, M. De Mariano, R. Russo, F. Cimmino, H. Hakonarson, G. P. Tonini, M. Devoto, J. M. Maris, and A.

Iolascon. 2013. "Replication of GWAS-identified neuroblastoma risk loci strengthens the role of BARD1 and affirms the cumulative effect of genetic variations on disease susceptibility." *Carcinogenesis* no. 34 (3):605-11. doi: 10.1093/carcin/bgs380.

Capasso, M., L. D. McDaniel, F. Cimmino, A. Cirino, D. Formicola, M. R. Russell, P. Raman, K. A. Cole, and S. J. Diskin. 2017. "The functional variant rs34330 of CDKN1B is associated with risk of neuroblastoma." *J Cell Mol Med* no. 21 (12):3224-3230. doi: 10.1111/jcmm.13226.

Capasso, M., A. Montella, M. Tirelli, T. Maiorino, S. Cantalupo, and A. Iolascon. 2020. "Genetic Predisposition to Solid Pediatric Cancers." *Front Oncol* no. 10:590033. doi: 10.3389/fonc.2020.590033.

Carracedo, A., L. C. Cantley, and P. P. Pandolfi. 2013. "Cancer metabolism: fatty acid oxidation in the limelight." *Nat Rev Cancer* no. 13 (4):227-32. doi: 10.1038/nrc3483.

Chang, X., M. Bakay, Y. Liu, J. Glessner, K. S. Rathi, C. Hou, H. Qu, Z. Vaksman, K. Nguyen, P. M. A. Sleiman, S. J. Diskin, J. M. Maris, and H. Hakonarson. 2020. "Mitochondrial DNA Haplogroups and Susceptibility to Neuroblastoma." *J Natl Cancer Inst* no. 112 (12):1259-1266. doi: 10.1093/jnci/djaa024.

Chang, X., Y. Zhao, C. Hou, J. Glessner, L. McDaniel, M. A. Diamond, K. Thomas, J. Li, Z. Wei, Y. Liu, Y. Guo, F. D. Mentch, H. Qiu, C. Kim, P. Evans, Z. Vaksman, S. J. Diskin, E. F. Attiyeh, P. Sleiman, J. M. Maris, and H. Hakonarson. 2017. "Common variants in MMP20 at 11q22.2 predispose to 11q deletion and neuroblastoma risk." *Nat Commun* no. 8 (1):569. doi: 10.1038/s41467-017-00408-8.

Cheung, N. K., and M. A. Dyer. 2013. "Neuroblastoma: developmental biology, cancer genomics and immunotherapy." *Nat Rev Cancer* no. 13 (6):397-411. doi: 10.1038/nrc3526.

Chung, C., T. Boterberg, J. Lucas, J. Panoff, D. Valteau-Couanet, B. Hero, R. Bagatell, and C. E. Hill-Kayser. 2021. "Neuroblastoma." *Pediatr Blood Cancer* no. 68 Suppl 2 (Suppl 2):e28473. doi: 10.1002/pbc.28473.

Cimmino, F., M. Avitabile, S. J. Diskin, Z. Vaksman, P. Pignataro, D. Formicola, A. Cardinale, A. Testori, J. Koster, C. de Torres, M. Devoto, J. M. Maris, A. Iolascon, and M. Capasso. 2018. "Fine mapping of 2q35 high-risk neuroblastoma locus reveals independent functional risk variants and suggests full-length BARD1 as tumor-suppressor." *Int J Cancer* no. 143 (11):2828-2837. doi: 10.1002/ijc.31822.

Cimmino, F., M. Avitabile, V. A. Lasorsa, L. Pezone, A. Cardinale, A. Montella, S. Cantalupo, A. Iolascon, and M. Capasso. 2020. "Functional characterization of full-length BARD1 strengthens its role as a tumor suppressor in neuroblastoma." *J Cancer* no. 11 (6):1495-1504. doi: 10.7150/jca.36164.

Cimmino, F., D. Formicola, and M. Capasso. 2017. "Dualistic Role of BARD1 in Cancer." *Genes (Basel)* no. 8 (12). doi: 10.3390/genes8120375.

Coco, S., J. Theissen, P. Scaruffi, S. Stigliani, S. Moretti, A. Oberthuer, F. Valdora, M. Fischer, F. Gallo, B. Hero, S. Bonassi, F. Berthold, and G. P. Tonini. 2012. "Age-dependent accumulation of genomic aberrations and deregulation of cell cycle and telomerase genes in metastatic neuroblastoma." *Int J Cancer* no. 131 (7):1591-600. doi: 10.1002/ijc.27432.

Colon, N. C., and D. H. Chung. 2011. "Neuroblastoma." *Adv Pediatr* no. 58 (1):297-311. doi: 10.1016/j.yapd.2011.03.011.

Corallo, D., M. Donadon, M. Pantile, V. Sidarovich, S. Cocchi, M. Ori, M. De Sarlo, S. Candiani, C. Frasson, M. Distel, A. Quattrone, C. Zanon, G. Basso, G. P. Tonini, and S. Aveic. 2020. "Correction to: LIN28B increases neural crest cell migration and leads to transformation of trunk sympathoadrenal precursors." *Cell Death Differ* no. 27 (4):1449. doi: 10.1038/s41418-019-0451-1.

Dai, W., H. Liu, X. Xu, J. Ge, S. Luo, D. Zhu, C. I. Amos, S. Fang, J. E. Lee, X. Li, H. Nan, C. Li, and Q. Wei. 2019. "Genetic variants in ELOVL2 and HSD17B12 predict melanoma-specific survival." *Int J Cancer* no. 145 (10):2619-2628. doi: 10.1002/ijc.32194.

De Bernardi, B., V. Mosseri, H. Rubie, V. Castel, A. Foot, R. Ladenstein, G. Laureys, M. Beck-Popovic, A. F. de Lacerda, A. D. Pearson, J. De Kraker, P. F. Ambros, Y. de Rycke, M. Conte, P. Bruzzi, J. Michon, and Siop Europe Neuroblastoma Group. 2008. "Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group." *Br J Cancer* no. 99 (7):1027-33. doi: 10.1038/sj.bjc.6604640.

De Mariano, M., R. Gallesio, M. Chierici, C. Furlanello, M. Conte, A. Garaventa, M. Croce, S. Ferrini, G. P. Tonini, and L. Longo. 2015. "Identification of GALNT14 as a novel neuroblastoma predisposition gene." *Oncotarget* no. 6 (28):26335-46. doi: 10.18632/oncotarget.4501.

Dedoni, S., M. C. Olianas, and P. Onali. 2010. "Interferon-beta induces apoptosis in human SH-SY5Y neuroblastoma cells through activation of JAK-STAT signaling and down-regulation of PI3K/Akt pathway." *J Neurochem* no. 115 (6):1421-33. doi: 10.1111/j.1471-4159.2010.07046.x.

Diskin, S. J., M. Capasso, M. Diamond, D. A. Oldridge, K. Conkrite, K. R. Bosse, M. R. Russell, A. Iolascon, H. Hakonarson, M. Devoto, and J. M. Maris. 2014. "Rare variants in TP53 and susceptibility to neuroblastoma." *J Natl Cancer Inst* no. 106 (4):dju047. doi: 10.1093/jnci/dju047.

Diskin, S. J., M. Capasso, R. W. Schnepp, K. A. Cole, E. F. Attiyeh, C. Hou, M. Diamond, E. L. Carpenter, C. Winter, H. Lee, J. Jagannathan, V. Latorre, A. Iolascon, H. Hakonarson, M. Devoto, and J. M. Maris. 2012. "Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma." *Nat Genet* no. 44 (10):1126-30. doi: 10.1038/ng.2387.

Du, L., L. Liu, C. Zhang, W. Cai, Y. Wu, J. Wang, and F. Lv. 2014. "Role of surgery in the treatment of patients with high-risk neuroblastoma who have a poor response to induction chemotherapy." *J Pediatr Surg* no. 49 (4):528-33. doi: 10.1016/j.jpedsurg.2013.11.061.

Egolf, L. E., Z. Vaksman, G. Lopez, J. L. Rokita, A. Modi, P. V. Basta, H. Hakonarson, A. F. Olshan, and S. J. Diskin. 2019. "Germline 16p11.2 Microdeletion Predisposes to Neuroblastoma." *Am J Hum Genet* no. 105 (3):658-668. doi: 10.1016/j.ajhg.2019.07.020.

Esposito, M. R., A. Binatti, M. Pantile, A. Coppe, K. Mazzocco, L. Longo, M. Capasso, V. A. Lasorsa, R. Luksch, S. Bortoluzzi, and G. P. Tonini. 2018. "Somatic mutations in specific and connected subpathways are associated with short neuroblastoma patients' survival and indicate proteins targetable at onset of disease." *Int J Cancer* no. 143 (10):2525-2536. doi: 10.1002/ijc.31748.

Feng, Y. X., E. S. Sokol, and P. B. Gupta. 2014. "The endoplasmic reticulum may be an Achilles' heel of cancer cells that have undergone an epithelial-to-mesenchymal transition." *Mol Cell Oncol* no. 1 (2):e961822. doi: 10.4161/23723548.2014.961822.

Frietze, S., R. Wang, L. Yao, Y. G. Tak, Z. Ye, M. Gaddis, H. Witt, P. J. Farnham, and V. X. Jin. 2012. "Cell type-specific binding patterns reveal that TCF7L2 can be tethered to the genome by association with GATA3." *Genome Biol* no. 13 (9):R52. doi: 10.1186/gb-2012-13-9-r52.

Fu, Y., T. Zou, X. Shen, P. J. Nelson, J. Li, C. Wu, J. Yang, Y. Zheng, C. Bruns, Y. Zhao, L. Qin, and Q. Dong. 2021. "Lipid metabolism in cancer progression and therapeutic strategies." *MedComm (2020)* no. 2 (1):27-59. doi: 10.1002/mco2.27.

Gallagher, M. D., and A. S. Chen-Plotkin. 2018. "The Post-GWAS Era: From Association to Function." *Am J Hum Genet* no. 102 (5):717-730. doi: 10.1016/j.ajhg.2018.04.002.

Gamazon, E. R., N. Pinto, A. Konkashbaev, H. K. Im, S. J. Diskin, W. B. London, J. M. Maris, M. E. Dolan, N. J. Cox, and S. L. Cohn. 2013. "Trans-population analysis of genetic mechanisms of ethnic disparities in neuroblastoma survival." *J Natl Cancer Inst* no. 105 (4):302-9. doi: 10.1093/jnci/djs503.

Gamble, L. D., S. Purgato, J. Murray, L. Xiao, D. M. T. Yu, K. M. Hanssen, F. M. Giorgi, D. R. Carter, A. J. Gifford, E. Valli, G. Milazzo, A. Kamili, C. Mayoh, B. Liu, G. Eden, S. Sarraf, S. Allan, S. Di Giacomo, C. L. Flemming, A. J. Russell, B. B. Cheung, A. Oberthuer, W. B. London, M. Fischer, T. N. Trahair, J. I. Fletcher, G. M. Marshall, D. S. Ziegler, M. D. Hogarty, M. R. Burns, G. Perini, M. D. Norris, and M. Haber. 2019. "Inhibition of polyamine synthesis and uptake reduces tumor progression and prolongs survival in mouse models of neuroblastoma." *Sci Transl Med* no. 11 (477). doi: 10.1126/scitranslmed.aau1099.

Grobner, S. N., B. C. Worst, J. Weischenfeldt, I. Buchhalter, K. Kleinheinz, V. A. Rudneva, P. D. Johann, G. P. Balasubramanian, M. Segura-Wang, S. Brabetz, S. Bender, B. Hutter, D. Sturm, E. Pfaff, D. Hubschmann, G. Zipprich, M. Heinold, J. Eils, C. Lawerenz, S. Erkek, S. Lambo, S. Waszak, C. Blattmann, A. Borkhardt, M. Kuhlen, A. Eggert, S. Fulda, M. Gessler, J. Wegert, R. Kappler, D. Baumhoer, S. Burdach, R. Kirschner-Schwabe, U. Kontny, A. E. Kulozik, D. Lohmann, S. Hettmer, C. Eckert, S. Bielack, M. Nathrath, C. Niemeyer, G. H. Richter, J. Schulte, R. Siebert, F. Westermann, J. J. Molenaar, G. Vassal, H. Witt, Icgc PedBrain-Seq Project, Icgc Mmml- Seq Project, B. Burkhardt, C. P. Kratz, O. Witt, C. M. van Tilburg, C. M. Kramm, G. Fleischhack, U. Dirksen, S. Rutkowski, M. Fruhwald, K. von Hoff, S. Wolf, T. Klingebiel, E. Koscielniak, P. Landgraf, J. Koster, A. C. Resnick, J. Zhang, Y. Liu, X. Zhou, A. J. Waanders, D. A. Zwijnenburg, P. Raman, B. Brors, U. D. Weber, P. A. Northcott, K. W. Pajtler, M. Kool, R. M. Piro, J. O. Korbel, M. Schlesner, R. Eils, D. T. W. Jones, P. Lichter, L. Chavez, M. Zapatka, and S. M. Pfister. 2018. "The landscape of genomic alterations across childhood cancers." *Nature* no. 555 (7696):321-327. doi: 10.1038/nature25480.

Harizi, H., J. B. Corcuff, and N. Gualde. 2008. "Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology." *Trends Mol Med* no. 14 (10):461-9. doi: 10.1016/j.molmed.2008.08.005.

Hiltunen, J. K., A. J. Kastaniotis, K. J. Autio, G. Jiang, Z. Chen, and T. Glumoff. 2019. "17B-hydroxysteroid dehydrogenases as acyl thioester metabolizing enzymes." *Mol Cell Endocrinol* no. 489:107-118. doi: 10.1016/j.mce.2018.11.012.

Hinds, D. A., L. L. Stuve, G. B. Nilsen, E. Halperin, E. Eskin, D. G. Ballinger, K. A. Frazer, and D. R. Cox. 2005. "Whole-genome patterns of common DNA variation in three human populations." *Science* no. 307 (5712):1072-9. doi: 10.1126/science.1105436.

Hirabayashi, Y. 2012. "A world of sphingolipids and glycolipids in the brain--novel functions of simple lipids modified with glucose." *Proc Jpn Acad Ser B Phys Biol Sci* no. 88 (4):129-43. doi: 10.2183/pjab.88.129.

Holder, P. G., S. A. Lim, C. S. Huang, P. Sharma, Y. S. Dagdas, B. Bulutoglu, and J. T. Sockolosky. 2022. "Engineering interferons and interleukins for cancer immunotherapy." *Adv Drug Deliv Rev* no. 182:114112. doi: 10.1016/j.addr.2022.114112.

Hou, R., Y. Yu, and J. Jiang. 2022. "Prostaglandin E2 in neuroblastoma: Targeting synthesis or signaling?" *Biomed Pharmacother* no. 156:113966. doi: 10.1016/j.biopha.2022.113966.

Hou, R., Y. Yu, M. N. Sluter, L. Li, J. Hao, J. Fang, J. Yang, and J. Jiang. 2022. "Targeting EP2 receptor with multifaceted mechanisms for high-risk neuroblastoma." *Cell Rep* no. 39 (12):111000. doi: 10.1016/j.celrep.2022.111000.

Hu, J., T. Fromel, and I. Fleming. 2018. "Angiogenesis and vascular stability in eicosanoids and cancer." *Cancer Metastasis Rev* no. 37 (2-3):425-438. doi: 10.1007/s10555-018-9732-2.

Hungate, E. A., M. A. Applebaum, A. D. Skol, Z. Vaksman, M. Diamond, L. McDaniel, S. L. Volchenboum, B. E. Stranger, J. M. Maris, S. J. Diskin, K. Onel, and S. L. Cohn. 2017. "Evaluation of Genetic Predisposition for MYCN-Amplified Neuroblastoma." *J Natl Cancer Inst* no. 109 (10). doi: 10.1093/jnci/djx093.

Janoueix-Lerosey, I., D. Lequin, L. Brugieres, A. Ribeiro, L. de Pontual, V. Combaret, V. Raynal, A. Puisieux, G. Schleiermacher, G. Pierron, D. Valteau-Couanet, T. Frebourg, J. Michon, S. Lyonnet, J. Amiel, and O. Delattre. 2008. "Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma." *Nature* no. 455 (7215):967-70. doi: 10.1038/nature07398.

Kato, H., and H. Nishitoh. 2015. "Stress responses from the endoplasmic reticulum in cancer." *Front Oncol* no. 5:93. doi: 10.3389/fonc.2015.00093.

Kemilainen, H., M. Adam, J. Maki-Jouppila, P. Damdimopoulou, A. E. Damdimopoulos, J. Kere, O. Hovatta, T. D. Laajala, T. Aittokallio, J. Adamski, H. Ryberg, C. Ohlsson, L. Strauss, and M. Poutanen. 2016. "The Hydroxysteroid (17beta) Dehydrogenase Family Gene HSD17B12 Is Involved in the Prostaglandin Synthesis Pathway, the Ovarian Function, and Regulation of Fertility." *Endocrinology* no. 157 (10):3719-3730. doi: 10.1210/en.2016-1252.

Kemilainen, H., K. Huhtinen, A. Auranen, O. Carpen, L. Strauss, and M. Poutanen. 2018. "The Expression of HSD17B12 Is Associated with COX-2 Expression and Is Increased in High-Grade Epithelial Ovarian Cancer." *Oncology* no. 94 (4):233-242. doi: 10.1159/000485624.

Kihara, A. 2012. "Very long-chain fatty acids: elongation, physiology and related disorders." *J Biochem* no. 152 (5):387-95. doi: 10.1093/jb/mvs105.
Koundouros, N., and G. Poulogiannis. 2020. "Reprogramming of fatty acid metabolism in cancer." *Br J Cancer* no. 122 (1):4-22. doi: 10.1038/s41416-019-0650-z.
Kratz, C. P., S. Rapisuwon, H. Reed, H. Hasle, and P. S. Rosenberg. 2011. "Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes." *Am J Med Genet C Semin Med Genet* no. 157C (2):83-9. doi: 10.1002/ajmg.c.30300.
Kulyte, A., A. Aman, R. J. Strawbridge, P. Arner, and I. A. Dahlman. 2022. "Genome-Wide Association Study Identifies Genetic Loci Associated With Fat Cell Number and Overlap With Genetic Risk Loci for Type 2 Diabetes." *Diabetes* no. 71 (6):1350-1362. doi: 10.2337/db21-0804.
L'Abbate, A., G. Macchia, P. D'Addabbo, A. Lonoce, D. Tolomeo, D. Trombetta, K. Kok, C. Bartenhagen, C. W. Whelan, O. Palumbo, M. Severgnini, I. Cifola, M. Dugas, M. Carella, G. De Bellis, M. Rocchi, L. Carbone, and C. T. Storlazzi. 2014. "Genomic organization and evolution of double minutes/homogeneously staining regions with MYC amplification in human cancer." *Nucleic Acids Res* no. 42 (14):9131-45. doi: 10.1093/nar/gku590.
Lasorsa, V. A., D. Formicola, P. Pignataro, F. Cimmino, F. M. Calabrese, J. Mora, M. R. Esposito, M. Pantile, C. Zanon, M. De Mariano, L. Longo, M. D. Hogarty, C. de Torres, G. P. Tonini, A. Iolascon, and M. Capasso. 2016. "Exome and deep sequencing of clinically aggressive neuroblastoma reveal somatic mutations that affect key pathways involved in cancer progression." *Oncotarget* no. 7 (16):21840-52. doi: 10.18632/oncotarget.8187.
Lerone, M., M. Ognibene, A. Pezzolo, G. Martucciello, F. Zara, M. Morini, and K. Mazzocco. 2021. "Molecular Genetics in Neuroblastoma Prognosis." *Children (Basel)* no. 8 (6). doi: 10.3390/children8060456.
Li, Z., H. Liu, and X. Luo. 2020. "Lipid droplet and its implication in cancer progression." *Am J Cancer Res* no. 10 (12):4112-4122.
Li, Z., and H. Zhang. 2016. "Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression." *Cell Mol Life Sci* no. 73 (2):377-92. doi: 10.1007/s00018-015-2070-4.
Lin, Y., Y. Meng, J. Zhang, L. Ma, L. Jiang, Y. Zhang, M. Yuan, A. Ren, W. Zhu, S. Li, Y. Shu, M. Du, and L. Zhu. 2020. "Functional genetic variant of HSD17B12 in the fatty acid biosynthesis pathway predicts the outcome of colorectal cancer." *J Cell Mol Med* no. 24 (24):14160-14170. doi: 10.1111/jcmm.16026.
Liu, H., G. Li, E. M. Sturgis, S. Shete, K. R. Dahlstrom, M. Du, C. I. Amos, D. C. Christiani, P. Lazarus, and Q. Wei. 2022. "Genetic variants in CYP2B6 and HSD17B12 associated with risk of squamous cell carcinoma of the head and neck." *Int J Cancer* no. 151 (4):553-564. doi: 10.1002/ijc.34023.
Lo Cunsolo, C., A. Iolascon, A. Cavazzana, R. Cusano, P. Strigini, K. Mazzocco, L. Giordani, L. Massimo, B. De Bernardi, M. Conte, and G. P. Tonini. 1999. "Neuroblastoma in two siblings supports the role of 1p36 deletion in tumor development." *Cancer Genet Cytogenet* no. 109 (2):126-30. doi: 10.1016/s0165-4608(98)00154-x.
London, W. B., R. P. Castleberry, K. K. Matthay, A. T. Look, R. C. Seeger, H. Shimada, P. Thorner, G. Brodeur, J. M. Maris, C. P. Reynolds, and S. L.

Cohn. 2005. "Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group." *J Clin Oncol* no. 23 (27):6459-65. doi: 10.1200/JCO.2005.05.571.

Luu-The, V., P. Tremblay, and F. Labrie. 2006. "Characterization of type 12 17beta-hydroxysteroid dehydrogenase, an isoform of type 3 17beta-hydroxysteroid dehydrogenase responsible for estradiol formation in women." *Mol Endocrinol* no. 20 (2):437-43. doi: 10.1210/me.2005-0058.

Maas, S. M., F. Vansenne, D. J. Kadouch, A. Ibrahim, J. Bliek, S. Hopman, M. M. Mannens, J. H. Merks, E. R. Maher, and R. C. Hennekam. 2016. "Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups." *Am J Med Genet A* no. 170 (9):2248-60. doi: 10.1002/ajmg.a.37801.

Mandula, J. K., S. Chang, E. Mohamed, R. Jimenez, R. A. Sierra-Mondragon, D. C. Chang, A. N. Obermayer, C. M. Moran-Segura, S. Das, J. A. Vazquez-Martinez, K. Prieto, A. Chen, K. S. M. Smalley, B. Czerniecki, P. Forsyth, R. C. Koya, B. Ruffell, J. R. Cubillos-Ruiz, D. H. Munn, T. I. Shaw, J. R. Conejo-Garcia, and P. C. Rodriguez. 2022. "Ablation of the endoplasmic reticulum stress kinase PERK induces paraptosis and type I interferon to promote anti-tumor T cell responses." *Cancer Cell* no. 40 (10):1145-1160 e9. doi: 10.1016/j.ccell.2022.08.016.

Maris, J. M., Y. P. Mosse, J. P. Bradfield, C. Hou, S. Monni, R. H. Scott, S. Asgharzadeh, E. F. Attiyeh, S. J. Diskin, M. Laudenslager, C. Winter, K. A. Cole, J. T. Glessner, C. Kim, E. C. Frackelton, T. Casalunovo, A. W. Eckert, M. Capasso, E. F. Rappaport, C. McConville, W. B. London, R. C. Seeger, N. Rahman, M. Devoto, S. F. Grant, H. Li, and H. Hakonarson. 2008. "Chromosome 6p22 locus associated with clinically aggressive neuroblastoma." *N Engl J Med* no. 358 (24):2585-93. doi: 10.1056/NEJMoa0708698.

Maris, J. M., M. J. Weiss, Y. Mosse, G. Hii, C. Guo, P. S. White, M. D. Hogarty, T. Mirensky, G. M. Brodeur, T. R. Rebbeck, M. Urbanek, and S. Shusterman. 2002. "Evidence for a hereditary neuroblastoma predisposition locus at chromosome 16p12-13." *Cancer Res* no. 62 (22):6651-8.

Matthay, K. K., J. M. Maris, G. Schleiermacher, A. Nakagawara, C. L. Mackall, L. Diller, and W. A. Weiss. 2016. "Neuroblastoma." *Nat Rev Dis Primers* no. 2:16078. doi: 10.1038/nrdp.2016.78.

Matthay, K. K., C. P. Reynolds, R. C. Seeger, H. Shimada, E. S. Adkins, D. Haas-Kogan, R. B. Gerbing, W. B. London, and J. G. Villablanca. 2009. "Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study." *J Clin Oncol* no. 27 (7):1007-13. doi: 10.1200/JCO.2007.13.8925.

Matthay, K. K., J. G. Villablanca, R. C. Seeger, D. O. Stram, R. E. Harris, N. K. Ramsay, P. Swift, H. Shimada, C. T. Black, G. M. Brodeur, R. B. Gerbing, and C. P. Reynolds. 1999. "Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group." *N Engl J Med* no. 341 (16):1165-73. doi: 10.1056/NEJM199910143411601.

Maurano, M. T., R. Humbert, E. Rynes, R. E. Thurman, E. Haugen, H. Wang, A. P. Reynolds, R. Sandstrom, H. Qu, J. Brody, A. Shafer, F. Neri, K. Lee, T.

Kutyavin, S. Stehling-Sun, A. K. Johnson, T. K. Canfield, E. Giste, M. Diegel, D. Bates, R. S. Hansen, S. Neph, P. J. Sabo, S. Heimfeld, A. Raubitschek, S. Ziegler, C. Cotsapas, N. Sotoodehnia, I. Glass, S. R. Sunyaev, R. Kaul, and J. A. Stamatoyannopoulos. 2012. "Systematic localization of common disease-associated variation in regulatory DNA." *Science* no. 337 (6099):1190-5. doi: 10.1126/science.1222794.

McDaniel, L. D., K. L. Conkrite, X. Chang, M. Capasso, Z. Vaksman, D. A. Oldridge, A. Zachariou, M. Horn, M. Diamond, C. Hou, A. Iolascon, H. Hakonarson, N. Rahman, M. Devoto, and S. J. Diskin. 2017. "Common variants upstream of MLF1 at 3q25 and within CPZ at 4p16 associated with neuroblastoma." *PLoS Genet* no. 13 (5):e1006787. doi: 10.1371/journal.pgen.1006787.

McNerney, K. O., S. A. Karageorgos, M. D. Hogarty, and H. Bassiri. 2020. "Enhancing Neuroblastoma Immunotherapies by Engaging iNKT and NK Cells." *Front Immunol* no. 11:873. doi: 10.3389/fimmu.2020.00873.

Mertens, A. C., Y. Yasui, J. P. Neglia, J. D. Potter, M. E. Nesbit, Jr., K. Ruccione, W. A. Smithson, and L. L. Robison. 2001. "Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study." *J Clin Oncol* no. 19 (13):3163-72. doi: 10.1200/JCO.2001.19.13.3163.

Moeller, G., and J. Adamski. 2006. "Multifunctionality of human 17beta-hydroxysteroid dehydrogenases." *Mol Cell Endocrinol* no. 248 (1-2):47-55. doi: 10.1016/j.mce.2005.11.031.

Mohamed, B., C. Mazeaud, M. Baril, D. Poirier, A. A. Sow, L. Chatel-Chaix, V. Titorenko, and D. Lamarre. 2020. "Very-long-chain fatty acid metabolic capacity of 17-beta-hydroxysteroid dehydrogenase type 12 (HSD17B12) promotes replication of hepatitis C virus and related flaviviruses." *Sci Rep* no. 10 (1):4040. doi: 10.1038/s41598-020-61051-w.

Molenaar, J. J., R. Domingo-Fernandez, M. E. Ebus, S. Lindner, J. Koster, K. Drabek, P. Mestdagh, P. van Sluis, L. J. Valentijn, J. van Nes, M. Broekmans, F. Haneveld, R. Volckmann, I. Bray, L. Heukamp, A. Sprussel, T. Thor, K. Kieckbusch, L. Klein-Hitpass, M. Fischer, J. Vandesompele, A. Schramm, M. M. van Noesel, L. Varesio, F. Speleman, A. Eggert, R. L. Stallings, H. N. Caron, R. Versteeg, and J. H. Schulte. 2012. "LIN28B induces neuroblastoma and enhances MYCN levels via let-7 suppression." *Nat Genet* no. 44 (11):1199-206. doi: 10.1038/ng.2436.

Molenaar, M. R., A. Jeucken, T. A. Wassenaar, C. H. A. van de Lest, J. F. Brouwers, and J. B. Helms. 2019. "LION/web: a web-based ontology enrichment tool for lipidomic data analysis." *Gigascience* no. 8 (6). doi: 10.1093/gigascience/giz061.

Mondal, T., P. K. Juvvuna, A. Kirkeby, S. Mitra, S. T. Kosalai, L. Traxler, F. Hertwig, S. Wernig-Zorc, C. Miranda, L. Deland, R. Volland, C. Bartenhagen, D. Bartsch, S. Bandaru, A. Engesser, S. Subhash, T. Martinsson, H. Caren, L. M. Akyurek, L. Kurian, M. Kanduri, M. Huarte, P. Kogner, M. Fischer, and C. Kanduri. 2018. "Sense-Antisense lncRNA Pair Encoded by Locus 6p22.3 Determines Neuroblastoma Susceptibility via the USP36-CHD7-SOX9 Regulatory Axis." *Cancer Cell* no. 33 (3):417-434 e7. doi: 10.1016/j.ccell.2018.01.020.

Moreno-Smith, M., G. Milazzo, L. Tao, B. Fekry, B. Zhu, M. A. Mohammad, S. Di Giacomo, R. Borkar, K. R. K. Reddy, M. Capasso, S. A. Vasudevan, P. Sumazin, J. Hicks, N. Putluri, G. Perini, K. Eckel-Mahan, T. P. Burris, and E.

Barbieri. 2021. "Restoration of the molecular clock is tumor suppressive in neuroblastoma." *Nat Commun* no. 12 (1):4006. doi: 10.1038/s41467-021-24196-4.

Mosse, Y. P., M. Laudenslager, D. Khazi, A. J. Carlisle, C. L. Winter, E. Rappaport, and J. M. Maris. 2004. "Germline PHOX2B mutation in hereditary neuroblastoma." *Am J Hum Genet* no. 75 (4):727-30. doi: 10.1086/424530.

Mosse, Y. P., M. Laudenslager, L. Longo, K. A. Cole, A. Wood, E. F. Attiyeh, M. J. Laquaglia, R. Sennett, J. E. Lynch, P. Perri, G. Laureys, F. Speleman, C. Kim, C. Hou, H. Hakonarson, A. Torkamani, N. J. Schork, G. M. Brodeur, G. P. Tonini, E. Rappaport, M. Devoto, and J. M. Maris. 2008. "Identification of ALK as a major familial neuroblastoma predisposition gene." *Nature* no. 455 (7215):930-5. doi: 10.1038/nature07261.

Mutesa, L., G. Pierquin, N. Janin, K. Segers, C. Thomee, M. Provenzi, and V. Bours. 2008. "Germline PTPN11 missense mutation in a case of Noonan syndrome associated with mediastinal and retroperitoneal neuroblastic tumors." *Cancer Genet Cytogenet* no. 182 (1):40-2. doi: 10.1016/j.cancergencyto.2007.12.005.

Nagasaki, S., T. Suzuki, Y. Miki, J. Akahira, K. Kitada, T. Ishida, H. Handa, N. Ohuchi, and H. Sasano. 2009. "17Beta-hydroxysteroid dehydrogenase type 12 in human breast carcinoma: a prognostic factor via potential regulation of fatty acid synthesis." *Cancer Res* no. 69 (4):1392-9. doi: 10.1158/0008-5472.CAN-08-0821.

Natsume, A., D. Ishii, T. Wakabayashi, T. Tsuno, H. Hatano, M. Mizuno, and J. Yoshida. 2005. "IFN-beta down-regulates the expression of DNA repair gene MGMT and sensitizes resistant glioma cells to temozolomide." *Cancer Res* no. 65 (17):7573-9. doi: 10.1158/0008-5472.CAN-05-0036.

Nguyen le, B., S. J. Diskin, M. Capasso, K. Wang, M. A. Diamond, J. Glessner, C. Kim, E. F. Attiyeh, Y. P. Mosse, K. Cole, A. Iolascon, M. Devoto, H. Hakonarson, H. K. Li, and J. M. Maris. 2011. "Phenotype restricted genome-wide association study using a gene-centric approach identifies three low-risk neuroblastoma susceptibility Loci." *PLoS Genet* no. 7 (3):e1002026. doi: 10.1371/journal.pgen.1002026.

Oei, L., K. Estrada, E. L. Duncan, C. Christiansen, C. T. Liu, B. L. Langdahl, B. Obermayer-Pietsch, J. A. Riancho, R. L. Prince, N. M. van Schoor, E. McCloskey, Y. H. Hsu, E. Evangelou, E. Ntzani, D. M. Evans, N. Alonso, L. B. Husted, C. Valero, J. L. Hernandez, J. R. Lewis, S. K. Kaptoge, K. Zhu, L. A. Cupples, C. Medina-Gomez, L. Vandenput, G. S. Kim, S. Hun Lee, M. C. Castano-Betancourt, E. H. Oei, J. Martinez, A. Daroszewska, M. van der Klift, D. Mellstrom, L. Herrera, M. K. Karlsson, A. Hofman, O. Ljunggren, H. A. Pols, L. Stolk, J. B. van Meurs, J. P. Ioannidis, M. C. Zillikens, P. Lips, D. Karasik, A. G. Uitterlinden, U. Styrkarsdottir, M. A. Brown, J. M. Koh, J. B. Richards, J. Reeve, C. Ohlsson, S. H. Ralston, D. P. Kiel, and F. Rivadeneira. 2014. "Genome-wide association study for radiographic vertebral fractures: a potential role for the 16q24 BMD locus." *Bone* no. 59:20-7.

Oliynyk, G., M. V. Ruiz-Perez, L. Sainero-Alcolado, J. Dzieran, H. Zirath, H. Gallart-Ayala, C. E. Wheelock, H. J. Johansson, R. Nilsson, J. Lehtio, and M. Arsenian-Henriksson. 2019. "MYCN-enhanced Oxidative and Glycolytic Metabolism Reveals Vulnerabilities for Targeting Neuroblastoma." *iScience* no. 21:188-204. doi: 10.1016/j.isci.2019.10.020.

Origone, P., R. Defferrari, K. Mazzocco, C. Lo Cunsolo, B. De Bernardi, and G. P. Tonini. 2003. "Homozygous inactivation of NF1 gene in a patient with familial NF1 and disseminated neuroblastoma." *Am J Med Genet A* no. 118A (4):309-13. doi: 10.1002/ajmg.a.10167.

Ozcan, A., H. Acer, S. Ciraci, H. Gumus, M. Karakukcu, T. Patiroglu, M. A. Ozdemir, and E. Unal. 2017. "Neuroblastoma in a Child With Wolf-Hirschhorn Syndrome." *J Pediatr Hematol Oncol* no. 39 (4):e224-e226. doi: 10.1097/MPH.0000000000000768.

Pandey, G. K., S. Mitra, S. Subhash, F. Hertwig, M. Kanduri, K. Mishra, S. Fransson, A. Ganeshram, T. Mondal, S. Bandaru, M. Ostensson, L. M. Akyurek, J. Abrahamsson, S. Pfeifer, E. Larsson, L. Shi, Z. Peng, M. Fischer, T. Martinsson, F. Hedborg, P. Kogner, and C. Kanduri. 2014. "The risk-associated long noncoding RNA NBAT-1 controls neuroblastoma progression by regulating cell proliferation and neuronal differentiation." *Cancer Cell* no. 26 (5):722-37. doi: 10.1016/j.ccell.2014.09.014.

Parsons, D. W., A. Roy, Y. Yang, T. Wang, S. Scollon, K. Bergstrom, R. A. Kerstein, S. Gutierrez, A. K. Petersen, A. Bavle, F. Y. Lin, D. H. Lopez-Terrada, F. A. Monzon, M. J. Hicks, K. W. Eldin, N. M. Quintanilla, A. M. Adesina, C. A. Mohila, W. Whitehead, A. Jea, S. A. Vasudevan, J. G. Nuchtern, U. Ramamurthy, A. L. McGuire, S. G. Hilsenbeck, J. G. Reid, D. M. Muzny, D. A. Wheeler, S. L. Berg, M. M. Chintagumpala, C. M. Eng, R. A. Gibbs, and S. E. Plon. 2016. "Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors." *JAMA Oncol* no. 2 (5):616-624. doi: 10.1001/jamaoncol.2015.5699.

Pattyn, A., X. Morin, H. Cremer, C. Goridis, and J. F. Brunet. 1999. "The homeobox gene Phox2b is essential for the development of autonomic neural crest derivatives." *Nature* no. 399 (6734):366-70. doi: 10.1038/20700.

Pei, D., W. Luther, W. Wang, B. H. Paw, R. A. Stewart, and R. E. George. 2013. "Distinct neuroblastoma-associated alterations of PHOX2B impair sympathetic neuronal differentiation in zebrafish models." *PLoS Genet* no. 9 (6):e1003533. doi: 10.1371/journal.pgen.1003533.

Peifer, M., F. Hertwig, F. Roels, D. Dreidax, M. Gartlgruber, R. Menon, A. Kramer, J. L. Roncaioli, F. Sand, J. M. Heuckmann, F. Ikram, R. Schmidt, S. Ackermann, A. Engesser, Y. Kahlert, W. Vogel, J. Altmuller, P. Nurnberg, J. Thierry-Mieg, D. Thierry-Mieg, A. Mariappan, S. Heynck, E. Mariotti, K. O. Henrich, C. Gloeckner, G. Bosco, I. Leuschner, M. R. Schweiger, L. Savelyeva, S. C. Watkins, C. Shao, E. Bell, T. Hofer, V. Achter, U. Lang, J. Theissen, R. Volland, M. Saadati, A. Eggert, B. de Wilde, F. Berthold, Z. Peng, C. Zhao, L. Shi, M. Ortmann, R. Buttner, S. Perner, B. Hero, A. Schramm, J. H. Schulte, C. Herrmann, R. J. O'Sullivan, F. Westermann, R. K. Thomas, and M. Fischer. 2015. "Telomerase activation by genomic rearrangements in high-risk neuroblastoma." *Nature* no. 526 (7575):700-4. doi: 10.1038/nature14980.

Perri, P., T. Bachetti, L. Longo, I. Matera, M. Seri, G. P. Tonini, and I. Ceccherini. 2005. "PHOX2B mutations and genetic predisposition to neuroblastoma." *Oncogene* no. 24 (18):3050-3. doi: 10.1038/sj.onc.1208532.

Perri, P., L. Longo, R. Cusano, C. M. McConville, S. A. Rees, M. Devoto, M. Conte, G. B. Ferrara, M. Seri, G. Romeo, and G. P. Tonini. 2002. "Weak linkage at

4p16 to predisposition for human neuroblastoma." *Oncogene* no. 21 (54):8356-60. doi: 10.1038/sj.onc.1206009.

Ponzoni, M., T. Bachetti, M. V. Corrias, C. Brignole, F. Pastorino, E. Calarco, V. Bensa, E. Giusto, I. Ceccherini, and P. Perri. 2022. "Recent advances in the developmental origin of neuroblastoma: an overview." *J Exp Clin Cancer Res* no. 41 (1):92. doi: 10.1186/s13046-022-02281-w.

Powers, J. T., K. M. Tsanov, D. S. Pearson, F. Roels, C. S. Spina, R. Ebright, M. Seligson, Y. de Soysa, P. Cahan, J. Theissen, H. C. Tu, A. Han, K. C. Kurek, G. S. LaPier, J. K. Osborne, S. J. Ross, M. Cesana, J. J. Collins, F. Berthold, and G. Q. Daley. 2016. "Multiple mechanisms disrupt the let-7 microRNA family in neuroblastoma." *Nature* no. 535 (7611):246-51. doi: 10.1038/nature18632.

Pugh, T. J., O. Morozova, E. F. Attiyeh, S. Asgharzadeh, J. S. Wei, D. Auclair, S. L. Carter, K. Cibulskis, M. Hanna, A. Kiezun, J. Kim, M. S. Lawrence, L. Lichenstein, A. McKenna, C. S. Pedamallu, A. H. Ramos, E. Shefler, A. Sivachenko, C. Sougnez, C. Stewart, A. Ally, I. Birol, R. Chiu, R. D. Corbett, M. Hirst, S. D. Jackman, B. Kamoh, A. H. Khodabakshi, M. Krzywinski, A. Lo, R. A. Moore, K. L. Mungall, J. Qian, A. Tam, N. Thiessen, Y. Zhao, K. A. Cole, M. Diamond, S. J. Diskin, Y. P. Mosse, A. C. Wood, L. Ji, R. Sposto, T. Badgett, W. B. London, Y. Moyer, J. M. Gastier-Foster, M. A. Smith, J. M. Guidry Auvil, D. S. Gerhard, M. D. Hogarty, S. J. Jones, E. S. Lander, S. B. Gabriel, G. Getz, R. C. Seeger, J. Khan, M. A. Marra, M. Meyerson, and J. M. Maris. 2013. "The genetic landscape of high-risk neuroblastoma." *Nat Genet* no. 45 (3):279-84. doi: 10.1038/ng.2529.

Raabe, E. H., M. Laudenslager, C. Winter, N. Wasserman, K. Cole, M. LaQuaglia, D. J. Maris, Y. P. Mosse, and J. M. Maris. 2008. "Prevalence and functional consequence of PHOX2B mutations in neuroblastoma." *Oncogene* no. 27 (4):469-76. doi: 10.1038/sj.onc.1210659.

Rantakari, P., H. Lagerbohm, M. Kaimainen, J. P. Suomela, L. Strauss, K. Sainio, P. Pakarinen, and M. Poutanen. 2010. "Hydroxysteroid (17beta) dehydrogenase 12 is essential for mouse organogenesis and embryonic survival." *Endocrinology* no. 151 (4):1893-901. doi: 10.1210/en.2009-0929.

Reiff, T., K. Tsarovina, A. Majdazari, M. Schmidt, I. del Pino, and H. Rohrer. 2010. "Neuroblastoma phox2b variants stimulate proliferation and dedifferentiation of immature sympathetic neurons." *J Neurosci* no. 30 (3):905-15. doi: 10.1523/JNEUROSCI.5368-09.2010.

Ren, P., M. Yue, D. Xiao, R. Xiu, L. Gan, H. Liu, and G. Qing. 2015. "ATF4 and N-Myc coordinate glutamine metabolism in MYCN-amplified neuroblastoma cells through ASCT2 activation." *J Pathol* no. 235 (1):90-100. doi: 10.1002/path.4429.

Rickman, D. S., R. Millon, A. De Reynies, E. Thomas, C. Wasylyk, D. Muller, J. Abecassis, and B. Wasylyk. 2008. "Prediction of future metastasis and molecular characterization of head and neck squamous-cell carcinoma based on transcriptome and genome analysis by microarrays." *Oncogene* no. 27 (51):6607-22. doi: 10.1038/onc.2008.251.

Rohrig, F., and A. Schulze. 2016. "The multifaceted roles of fatty acid synthesis in cancer." *Nat Rev Cancer* no. 16 (11):732-749. doi: 10.1038/nrc.2016.89.

Rosati, S. F., R. F. Williams, L. C. Nunnally, M. C. McGee, T. L. Sims, L. Tracey, J. Zhou, M. Fan, C. Y. Ng, A. C. Nathwani, C. F. Stewart, L. M. Pfeffer, and A.

M. Davidoff. 2008. "IFN-beta sensitizes neuroblastoma to the antitumor activity of temozolomide by modulating O6-methylguanine DNA methyltransferase expression." *Mol Cancer Ther* no. 7 (12):3852-8. doi: 10.1158/1535-7163.MCT-08-0806.

Ruiz-Perez, M. V., L. Sainero-Alcolado, G. Oliynyk, I. Matuschek, N. Balboni, Sjka Ubhayasekera, M. T. Snaebjornsson, K. Makowski, K. Aaltonen, D. Bexell, D. Serra, R. Nilsson, J. Bergquist, A. Schulze, and M. Arsenian-Henriksson. 2021. "Inhibition of fatty acid synthesis induces differentiation and reduces tumor burden in childhood neuroblastoma." *iScience* no. 24 (2):102128. doi: 10.1016/j.isci.2021.102128.

Russell, M. R., A. Penikis, D. A. Oldridge, J. R. Alvarez-Dominguez, L. McDaniel, M. Diamond, O. Padovan, P. Raman, Y. Li, J. S. Wei, S. Zhang, J. Gnanchandran, R. Seeger, S. Asgharzadeh, J. Khan, S. J. Diskin, J. M. Maris, and K. A. Cole. 2015. "CASC15-S Is a Tumor Suppressor lncRNA at the 6p22 Neuroblastoma Susceptibility Locus." *Cancer Res* no. 75 (15):3155-66. doi: 10.1158/0008-5472.CAN-14-3613.

Ryser, S., E. Dizin, C. E. Jefford, B. Delaval, S. Gagos, A. Christodoulidou, K. H. Krause, D. Birnbaum, and I. Irminger-Finger. 2009. "Distinct roles of BARD1 isoforms in mitosis: full-length BARD1 mediates Aurora B degradation, cancer-associated BARD1beta scaffolds Aurora B and BRCA2." *Cancer Res* no. 69 (3):1125-34. doi: 10.1158/0008-5472.CAN-08-2134.

Saini, R. K., and Y. S. Keum. 2018. "Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance - A review." *Life Sci* no. 203:255-267. doi: 10.1016/j.lfs.2018.04.049.

Sakurai, N., Y. Miki, T. Suzuki, K. Watanabe, T. Narita, K. Ando, T. M. Yung, D. Aoki, H. Sasano, and H. Handa. 2006. "Systemic distribution and tissue localizations of human 17beta-hydroxysteroid dehydrogenase type 12." *J Steroid Biochem Mol Biol* no. 99 (4-5):174-81. doi: 10.1016/j.jsbmb.2006.01.010.

Saloniemi, T., H. Jokela, L. Strauss, P. Pakarinen, and M. Poutanen. 2012. "The diversity of sex steroid action: novel functions of hydroxysteroid (17beta) dehydrogenases as revealed by genetically modified mouse models." *J Endocrinol* no. 212 (1):27-40. doi: 10.1530/JOE-11-0315.

Sassa, T., and A. Kihara. 2014. "Metabolism of very long-chain Fatty acids: genes and pathophysiology." *Biomol Ther (Seoul)* no. 22 (2):83-92. doi: 10.4062/biomolther.2014.017.

Schaub, M. A., A. P. Boyle, A. Kundaje, S. Batzoglou, and M. Snyder. 2012. "Linking disease associations with regulatory information in the human genome." *Genome Res* no. 22 (9):1748-59. doi: 10.1101/gr.136127.111.

Schimke, R. N., D. L. Collins, and C. A. Stolle. 2010. "Paraganglioma, neuroblastoma, and a SDHB mutation: Resolution of a 30-year-old mystery." *Am J Med Genet A* no. 152A (6):1531-5. doi: 10.1002/ajmg.a.33384.

Schleiermacher, G., J. Michon, A. Ribeiro, G. Pierron, V. Mosseri, H. Rubie, C. Munzer, J. Benard, N. Auger, V. Combaret, I. Janoueix-Lerosey, A. Pearson, D. A. Tweddle, N. Bown, M. Gerrard, K. Wheeler, R. Noguera, E. Villamon, A. Canete, V. Castel, B. Marques, A. de Lacerda, G. P. Tonini, K. Mazzocco, R. Defferrari, B. de Bernardi, A. di Cataldo, N. van Roy, B. Brichard, R. Ladenstein, I. Ambros, P. Ambros, K. Beiske, O. Delattre, and J. Couturier. 2011. "Segmental chromosomal alterations lead to a higher risk of relapse in

infants with MYCN-non-amplified localised unresectable/disseminated neuroblastoma (a SIOPEN collaborative study)." *Br J Cancer* no. 105 (12):1940-8. doi: 10.1038/bjc.2011.472.

Schleiermacher, G., V. Mosseri, W. B. London, J. M. Maris, G. M. Brodeur, E. Attiyeh, M. Haber, J. Khan, A. Nakagawara, F. Speleman, R. Noguera, G. P. Tonini, M. Fischer, I. Ambros, T. Monclair, K. K. Matthay, P. Ambros, S. L. Cohn, and A. D. Pearson. 2012. "Segmental chromosomal alterations have prognostic impact in neuroblastoma: a report from the INRG project." *Br J Cancer* no. 107 (8):1418-22. doi: 10.1038/bjc.2012.375.

Schnepp, R. W., P. Khurana, E. F. Attiyeh, P. Raman, S. E. Chodosh, D. A. Oldridge, M. E. Gagliardi, K. L. Conkrite, S. Asgharzadeh, R. C. Seeger, B. B. Madison, A. K. Rustgi, J. M. Maris, and S. J. Diskin. 2015. "A LIN28B-RAN-AURKA Signaling Network Promotes Neuroblastoma Tumorigenesis." *Cancer Cell* no. 28 (5):599-609. doi: 10.1016/j.ccell.2015.09.012.

Serra, A., B. Haberle, I. R. Konig, R. Kappler, M. Suttorp, H. K. Schackert, D. Roesner, and G. Fitze. 2008. "Rare occurrence of PHOX2b mutations in sporadic neuroblastomas." *J Pediatr Hematol Oncol* no. 30 (10):728-32. doi: 10.1097/MPH.0b013e3181772141.

Smith, E. I., G. M. Haase, R. C. Seeger, and G. M. Brodeur. 1989. "A surgical perspective on the current staging in neuroblastoma--the International Neuroblastoma Staging System proposal." *J Pediatr Surg* no. 24 (4):386-90. doi: 10.1016/s0022-3468(89)80277-5.

Smith, V., and J. Foster. 2018. "High-Risk Neuroblastoma Treatment Review." *Children (Basel)* no. 5 (9). doi: 10.3390/children5090114.

Song, D., G. Liu, V. Luu-The, D. Zhao, L. Wang, H. Zhang, G. Xueling, S. Li, L. Desy, F. Labrie, and G. Pelletier. 2006. "Expression of aromatase and 17beta-hydroxysteroid dehydrogenase types 1, 7 and 12 in breast cancer. An immunocytochemical study." *J Steroid Biochem Mol Biol* no. 101 (2-3):136-44. doi: 10.1016/j.jsbmb.2006.06.015.

Song, L., S. Asgharzadeh, J. Salo, K. Engell, H. W. Wu, R. Sposto, T. Ara, A. M. Silverman, Y. A. DeClerck, R. C. Seeger, and L. S. Metelitsa. 2009. "Valpha24-invariant NKT cells mediate antitumor activity via killing of tumor-associated macrophages." *J Clin Invest* no. 119 (6):1524-36. doi: 10.1172/JCI37869.

Stigliani, S., S. Coco, S. Moretti, A. Oberthuer, M. Fischer, J. Theissen, F. Gallo, A. Garavent, F. Berthold, S. Bonassi, G. P. Tonini, and P. Scaruffi. 2012. "High genomic instability predicts survival in metastatic high-risk neuroblastoma." *Neoplasia* no. 14 (9):823-32. doi: 10.1593/neo.121114.

Studies, Nci-Nhgri Working Group on Replication in Association, S. J. Chanock, T. Manolio, M. Boehnke, E. Boerwinkle, D. J. Hunter, G. Thomas, J. N. Hirschhorn, G. Abecasis, D. Altshuler, J. E. Bailey-Wilson, L. D. Brooks, L. R. Cardon, M. Daly, P. Donnelly, J. F. Fraumeni, Jr., N. B. Freimer, D. S. Gerhard, C. Gunter, A. E. Guttmacher, M. S. Guyer, E. L. Harris, J. Hoh, R. Hoover, C. A. Kong, K. R. Merikangas, C. C. Morton, L. J. Palmer, E. G. Phimister, J. P. Rice, J. Roberts, C. Rotimi, M. A. Tucker, K. J. Vogan, S. Wacholder, E. M. Wijsman, D. M. Winn, and F. S. Collins. 2007. "Replicating genotype-phenotype associations." *Nature* no. 447 (7145):655-60. doi: 10.1038/447655a.

Sun, T., W. K. Oh, S. Jacobus, M. Regan, M. Pomerantz, M. L. Freedman, G. S. Lee, and P. W. Kantoff. 2011. "The impact of common genetic variations in genes of the sex hormone metabolic pathways on steroid hormone levels and prostate cancer aggressiveness." *Cancer Prev Res (Phila)* no. 4 (12):2044-50. doi: 10.1158/1940-6207.CAPR-11-0283.

Szajnik, M., M. J. Szczepanski, E. Elishaev, C. Visus, D. Lenzner, M. Zabel, M. Glura, A. B. DeLeo, and T. L. Whiteside. 2012. "17beta Hydroxysteroid dehydrogenase type 12 (HSD17B12) is a marker of poor prognosis in ovarian carcinoma." *Gynecol Oncol* no. 127 (3):587-94. doi: 10.1016/j.ygyno.2012.08.010.

Takita, J. 2021. "Molecular Basis and Clinical Features of Neuroblastoma." *JMA J* no. 4 (4):321-331. doi: 10.31662/jmaj.2021-0077.

Tao, L., M. A. Mohammad, G. Milazzo, M. Moreno-Smith, T. D. Patel, B. Zorman, A. Badachhape, B. E. Hernandez, A. B. Wolf, Z. Zeng, J. H. Foster, S. Aloisi, P. Sumazin, Y. Zu, J. Hicks, K. B. Ghaghada, N. Putluri, G. Perini, C. Coarfa, and E. Barbieri. 2022. "MYCN-driven fatty acid uptake is a metabolic vulnerability in neuroblastoma." *Nat Commun* no. 13 (1):3728. doi: 10.1038/s41467-022-31331-2.

Tatton-Brown, K., A. Murray, S. Hanks, J. Douglas, R. Armstrong, S. Banka, L. M. Bird, C. L. Clericuzio, V. Cormier-Daire, T. Cushing, F. Flinter, M. L. Jacquemont, S. Joss, E. Kinning, S. A. Lynch, A. Magee, V. McConnell, A. Medeira, K. Ozono, M. Patton, J. Rankin, D. Shears, M. Simon, M. Splitt, V. Strenger, K. Stuurman, C. Taylor, H. Titheradge, L. Van Maldergem, I. K. Temple, T. Cole, S. Seal, Consortium Childhood Overgrowth, and N. Rahman. 2013. "Weaver syndrome and EZH2 mutations: Clarifying the clinical phenotype." *Am J Med Genet A* no. 161A (12):2972-80. doi: 10.1002/ajmg.a.36229.

Testori, A., V. A. Lasorsa, F. Cimmino, S. Cantalupo, A. Cardinale, M. Avitabile, G. Limongelli, M. G. Russo, S. Diskin, J. Maris, M. Devoto, B. Keavney, H. J. Cordell, A. Iolascon, and M. Capasso. 2019. "Exploring Shared Susceptibility between Two Neural Crest Cells Originating Conditions: Neuroblastoma and Congenital Heart Disease." *Genes (Basel)* no. 10 (9). doi: 10.3390/genes10090663.

Tolbert, V. P., and K. K. Matthay. 2018. "Neuroblastoma: clinical and biological approach to risk stratification and treatment." *Cell Tissue Res* no. 372 (2):195-209. doi: 10.1007/s00441-018-2821-2.

Tonini, G. P. 2017. "Growth, progression and chromosome instability of Neuroblastoma: a new scenario of tumorigenesis?" *BMC Cancer* no. 17 (1):20. doi: 10.1186/s12885-016-2986-6.

Tonini, G. P., L. Boni, A. Pession, D. Rogers, A. Iolascon, G. Basso, L. Cordero di Montezemolo, F. Casale, A. Pession, P. Perri, K. Mazzocco, P. Scaruffi, C. Lo Cunsolo, N. Marchese, C. Milanaccio, M. Conte, P. Bruzzi, and B. De Bernardi. 1997. "MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4s: the Italian experience with 295 children." *J Clin Oncol* no. 15 (1):85-93. doi: 10.1200/JCO.1997.15.1.85.

Tonini, G. P., and M. Capasso. 2020. "Genetic predisposition and chromosome instability in neuroblastoma." *Cancer Metastasis Rev* no. 39 (1):275-285. doi: 10.1007/s10555-020-09843-4.

Tonini, G. P., C. Lo Cunsolo, R. Cusano, A. Iolascon, M. Dagnino, M. Conte, C. Milanaccio, B. De Bernardi, K. Mazzocco, and P. Scaruffi. 1997. "Loss of heterozygosity for chromosome 1p in familial neuroblastoma." *Eur J Cancer* no. 33 (12):1953-6. doi: 10.1016/s0959-8049(97)00288-8.

Totaro, F., F. Cimmino, P. Pignataro, G. Acierno, M. De Mariano, L. Longo, G. P. Tonini, A. Iolascon, and M. Capasso. 2013. "Impact of interleukin-6 -174 G>C gene promoter polymorphism on neuroblastoma." *PLoS One* no. 8 (10):e76810. doi: 10.1371/journal.pone.0076810.

Trochet, D., F. Bourdeaut, I. Janoueix-Lerosey, A. Deville, L. de Pontual, G. Schleiermacher, C. Coze, N. Philip, T. Frebourg, A. Munnich, S. Lyonnet, O. Delattre, and J. Amiel. 2004. "Germline mutations of the paired-like homeobox 2B (PHOX2B) gene in neuroblastoma." *Am J Hum Genet* no. 74 (4):761-4. doi: 10.1086/383253.

Tsachaki, M., P. Strauss, A. Dunkel, H. Navratilova, N. Mladenovic, and A. Odermatt. 2020. "Impact of 17beta-HSD12, the 3-ketoacyl-CoA reductase of long-chain fatty acid synthesis, on breast cancer cell proliferation and migration." *Cell Mol Life Sci* no. 77 (6):1153-1175. doi: 10.1007/s00018-019-03227-w.

Uhlen, M., C. Zhang, S. Lee, E. Sjostedt, L. Fagerberg, G. Bidkhori, R. Benfeitas, M. Arif, Z. Liu, F. Edfors, K. Sanli, K. von Feilitzen, P. Oksvold, E. Lundberg, S. Hober, P. Nilsson, J. Mattsson, J. M. Schwenk, H. Brunnstrom, B. Glimelius, T. Sjoblom, P. H. Edqvist, D. Djureinovic, P. Micke, C. Lindskog, A. Mardinoglu, and F. Ponten. 2017. "A pathology atlas of the human cancer transcriptome." *Science* no. 357 (6352). doi: 10.1126/science.aan2507.

Valentijn, L. J., J. Koster, D. A. Zwijnenburg, N. E. Hasselt, P. van Sluis, R. Volckmann, M. M. van Noesel, R. E. George, G. A. Tytgat, J. J. Molenaar, and R. Versteeg. 2015. "TERT rearrangements are frequent in neuroblastoma and identify aggressive tumors." *Nat Genet* no. 47 (12):1411-4. doi: 10.1038/ng.3438.

van Limpt, V., A. Schramm, A. van Lakeman, P. Sluis, A. Chan, M. van Noesel, F. Baas, H. Caron, A. Eggert, and R. Versteeg. 2004. "The Phox2B homeobox gene is mutated in sporadic neuroblastomas." *Oncogene* no. 23 (57):9280-8. doi: 10.1038/sj.onc.1208157.

Vandesompele, J., M. Baudis, K. De Preter, N. Van Roy, P. Ambros, N. Bown, C. Brinkschmidt, H. Christiansen, V. Combaret, M. Lastowska, J. Nicholson, A. O'Meara, D. Plantaz, R. Stallings, B. Brichard, C. Van den Broecke, S. De Bie, A. De Paepe, G. Laureys, and F. Speleman. 2005. "Unequivocal delineation of clinicogenetic subgroups and development of a new model for improved outcome prediction in neuroblastoma." *J Clin Oncol* no. 23 (10):2280-99. doi: 10.1200/JCO.2005.06.104.

Vannucchi, S., M. V. Chiantore, G. Mangino, Z. A. Percario, E. Affabris, G. Fiorucci, and G. Romeo. 2007. "Perspectives in biomolecular therapeutic intervention in cancer: from the early to the new strategies with type I interferons." *Curr Med Chem* no. 14 (6):667-79. doi: 10.2174/092986707780059616.

Wang, D., and R. N. Dubois. 2010. "Eicosanoids and cancer." *Nat Rev Cancer* no. 10 (3):181-93. doi: 10.1038/nrc2809.

Wang, K., S. J. Diskin, H. Zhang, E. F. Attiyeh, C. Winter, C. Hou, R. W. Schnepp, M. Diamond, K. Bosse, P. A. Mayes, J. Glessner, C. Kim, E. Frackelton, M. Garris, Q. Wang, W. Glaberson, R. Chiavacci, L. Nguyen, J. Jagannathan, N. Saeki, H. Sasaki, S. F. Grant, A. Iolascon, Y. P. Mosse, K. A. Cole, H. Li, M.

Devoto, P. W. McGrady, W. B. London, M. Capasso, N. Rahman, H. Hakonarson, and J. M. Maris. 2011. "Integrative genomics identifies LMO1 as a neuroblastoma oncogene." *Nature* no. 469 (7329):216-20. doi: 10.1038/nature09609.

Welter, D., J. MacArthur, J. Morales, T. Burdett, P. Hall, H. Junkins, A. Klemm, P. Flicek, T. Manolio, L. Hindorff, and H. Parkinson. 2014. "The NHGRI GWAS Catalog, a curated resource of SNP-trait associations." *Nucleic Acids Res* no. 42 (Database issue):D1001-6. doi: 10.1093/nar/gkt1229.

Xia, Y., B. Ye, J. Ding, Y. Yu, A. Alptekin, M. Thangaraju, P. D. Prasad, Z. C. Ding, E. J. Park, J. H. Choi, B. Gao, O. Fiehn, C. Yan, Z. Dong, Y. Zha, and H. F. Ding. 2019. "Metabolic Reprogramming by MYCN Confers Dependence on the Serine-Glycine-One-Carbon Biosynthetic Pathway." *Cancer Res* no. 79 (15):3837-3850. doi: 10.1158/0008-5472.CAN-18-3541.

Yalcin, B., L. C. Kremer, H. N. Caron, and E. C. van Dalen. 2013. "High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma." *Cochrane Database Syst Rev* (8):CD006301. doi: 10.1002/14651858.CD006301.pub3.

Yeh, I. T., R. E. Lenci, Y. Qin, K. Buddavarapu, A. H. Ligon, E. Leteurtre, C. Do Cao, C. Cardot-Bauters, P. Pigny, and P. L. Dahia. 2008. "A germline mutation of the KIF1B beta gene on 1p36 in a family with neural and nonneural tumors." *Hum Genet* no. 124 (3):279-85. doi: 10.1007/s00439-008-0553-1.

Yu, A. L., A. L. Gilman, M. F. Ozkaynak, W. B. London, S. G. Kreissman, H. X. Chen, M. Smith, B. Anderson, J. G. Villablanca, K. K. Matthay, H. Shimada, S. A. Grupp, R. Seeger, C. P. Reynolds, A. Buxton, R. A. Reisfeld, S. D. Gillies, S. L. Cohn, J. M. Maris, P. M. Sondel, and Group Children's Oncology. 2010. "Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma." *N Engl J Med* no. 363 (14):1324-34. doi: 10.1056/NEJMoa0911123.

Zafar, A., W. Wang, G. Liu, X. Wang, W. Xian, F. McKeon, J. Foster, J. Zhou, and R. Zhang. 2021. "Molecular targeting therapies for neuroblastoma: Progress and challenges." *Med Res Rev* no. 41 (2):961-1021. doi: 10.1002/med.21750.

Zeineldin, M., A. G. Patel, and M. A. Dyer. 2022. "Neuroblastoma: When differentiation goes awry." *Neuron* no. 110 (18):2916-2928. doi: 10.1016/j.neuron.2022.07.012.

Zhang, J., M. F. Walsh, G. Wu, M. N. Edmonson, T. A. Gruber, J. Easton, D. Hedges, X. Ma, X. Zhou, D. A. Yergeau, M. R. Wilkinson, B. Vadodaria, X. Chen, R. B. McGee, S. Hines-Dowell, R. Nuccio, E. Quinn, S. A. Shurtleff, M. Rusch, A. Patel, J. B. Becksfort, S. Wang, M. S. Weaver, L. Ding, E. R. Mardis, R. K. Wilson, A. Gajjar, D. W. Ellison, A. S. Pappo, C. H. Pui, K. E. Nichols, and J. R. Downing. 2015. "Germline Mutations in Predisposition Genes in Pediatric Cancer." *N Engl J Med* no. 373 (24):2336-2346. doi: 10.1056/NEJMoa1508054.

Zhang, T., A. A. de Waard, M. Wuhrer, and R. M. Spaapen. 2019. "The Role of Glycosphingolipids in Immune Cell Functions." *Front Immunol* no. 10:90. doi: 10.3389/fimmu.2019.00090.

Zhang, Z., Y. Zou, J. Zhu, R. Zhang, T. Yang, F. Wang, H. Xia, J. He, and Z. Feng. 2017. "HSD17B12 gene rs11037575 C>T polymorphism confers

neuroblastoma susceptibility in a Southern Chinese population." *Onco Targets Ther* no. 10:1969-1975. doi: 10.2147/OTT.S136006.

Zhu, S., X. Zhang, N. Weichert-Leahey, Z. Dong, C. Zhang, G. Lopez, T. Tao, S. He, A. C. Wood, D. Oldridge, C. Y. Ung, J. H. van Ree, A. Khan, B. M. Salazar, E. Lummertz da Rocha, M. W. Zimmerman, F. Guo, H. Cao, X. Hou, S. J. Weroha, A. R. Perez-Atayde, D. S. Neuberg, A. Meves, M. A. McNiven, J. M. van Deursen, H. Li, J. M. Maris, and A. T. Look. 2017. "LMO1 Synergizes with MYCN to Promote Neuroblastoma Initiation and Metastasis." *Cancer Cell* no. 32 (3):310-323 e5. doi: 10.1016/j.ccell.2017.08.002.

Zirath, H., A. Frenzel, G. Oliynyk, L. Segerstrom, U. K. Westermark, K. Larsson, M. Munksgaard Persson, K. Hultenby, J. Lehtio, C. Einvik, S. Pahlman, P. Kogner, P. J. Jakobsson, and M. A. Henriksson. 2013. "MYC inhibition induces metabolic changes leading to accumulation of lipid droplets in tumor cells." *Proc Natl Acad Sci U S A* no. 110 (25):10258-63. doi: 10.1073/pnas.1222404110.