Joining forces in endocrine cancer genetics: molecular testing, surveillance and treatment decision making in clinical practice

Tuin, K. van der

APPENDIX

LIST OF PUBLICATIONS

van der Tuin K, Ventayol Garcia M, Corver WE, Khalifa MN, Ruano Neto D, Corssmit EPM, Hes FJ, Links TP, Smit JWA, Plantinga TS, Kapiteijn E, van Wezel T, Morreau H. Targetable gene fusions identified in radioactive iodine refractory advanced thyroid carcinoma. Eur J Endocrinol. 2019 Apr 1;180(4):235-241.

van der Sluijs PJ, Aten E, Barge-Schaapveld DQCM, Bijlsma EK, Bökenkamp-Gramann R, Donker Kaat L, van Doorn R, van de Putte DF, van Haeringen A, Ten Harkel ADJ, Hilhorst-Hofstee Y, Hoffer MJV, den Hollander NS, van Ierland Y, Koopmans M, Kriek M, Moghadasi S, Nibbeling EAR, Peeters-Scholte CMPCD, Potjer TP, van Rij M, Ruivenkamp CAL, Rutten JW, Steggerda SJ, Suerink M, Tan RNGB, **van der Tuin K**, Visser R, van der Werf-'t Lam AS, Williams M, Witlox R, Santen GWE. Putting genome-wide sequencing in neonates into perspective. Genet Med. 2019 May;21(5):1074-1082.

van der Tuin K, de Kock L, Kamping EJ, Hannema SE, Pouwels MM, Niedziela M, van Wezel T, Hes FJ, Jongmans MC, Foulkes WD, Morreau H. Clinical and Molecular Characteristics May Alter Treatment Strategies of Thyroid Malignancies in DICER1 Syndrome. J Clin Endocrinol Metab. 2019 Feb 1;104(2):277-284

van der Tuin K, Mensenkamp AR, Tops CMJ, Corssmit EPM, Dinjens WN, van de Horst-Schrivers AN, Jansen JC, de Jong MM, Kunst HPM, Kusters B, Leter EM, Morreau H, van Nesselrooij BMP, Oldenburg RA, Spruijt L, Hes FJ, Timmers HJLM. Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study. J Clin Endocrinol Metab. 2018 Feb 1;103(2):438-445

van der Tuin K, Tops CMJ, Adank MA, Cobben JM, Hamdy NAT, Jongmans MC, Menko FH, van Nesselrooij BPM, Netea-Maier RT, Oosterwijk JC, Valk GD, Wolffenbuttel BHR, Hes FJ, Morreau H. CDC73-Related Disorders: Clinical Manifestations and Case Detection in Primary Hyperparathyroidism. J Clin Endocrinol Metab. 2017 Dec 1;102(12):4534-4540

van der Tuin K, Hofland N, Appelman-Dijkstra NM, van der Luijt RB, van Wezel T, Morreau H, Hes FJ. A 93-year-old MEN2A mutation carrier without Medullary Thyroid Carcinoma: a case report and overview of the literature. Cancer Research Frontiers. 2016 Feb; 2(1): 60-66

van der Tuin K, Hannema SE, Houdijk EC, Losekoot M, de Koning EJ, Breuning MH. Maturity-onset diabetes of the young. Ned Tijdschr Geneeskd. 2015;159:A9247 [in Dutch].

Maas SM, Shaw AC, Bikker H, Lüdecke HJ, **van der Tuin K**, Badura-Stronka M, Belligni E, Biamino E, Bonati MT, Carvalho DR, Cobben J, de Man SA, Den Hollander NS, Di Donato N, Garavelli L, Grønborg S, Herkert JC, Hoogeboom AJ, Jamsheer A, Latos-Bielenska A, Maat-Kievit A, Magnani C, Marcelis C, Mathijssen IB, Nielsen M, Otten E, Ousager LB, Pilch J, Plomp A, Poke G, Poluha A, Posmyk R, Rieubland C, Silengo M, Simon M, Steichen E, Stumpel C, Szakszon K, Polonkai E, van den Ende J, van der Steen A, van Essen T, van Haeringen A, van Hagen JM, Verheij JB, Mannens MM, Hennekam RC. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal syndrome. Eur J Med Genet. 2015 May;58(5):279-92

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GENETIC GLOSSARY

Autosomal dominant inheritance: refers to disorders caused by mutated genes located on the non-sex chromosomes (autosomes), thereby affecting both males and females. The disease or mutant alleles are dominant to the wild-type alleles, so the disorder is manifest in the heterozygote (i.e., an individual who possesses both the wild-type and the mutant allele) and shows vertical transmission. This disease can also occur as a new condition in a child when neither parent has the abnormal gene (*de novo*). A person with an autosomal dominant disorder has a 50% chance of having an affected child. Children who do not inherit the abnormal gene will not develop or pass on the disease.

Mutation carrier: is used to indicate an individual who has one correct gene copy and one mutated gene copy. The term is used to indicate an individual with a heterozygote germline mutation related to a monogenetic disorder. In this situation mutation carriers are at increased risk to develop a certain disease. The term is also used to indicate carriers of a recessive mutation, they are usually not affected but they are at risk for passing on the mutated gene to their offspring.

De novo mutation: is a genetic alteration that is present for the first time in one family member as a result of a variant in a germ cell (egg or sperm) of one of the parents, or a variant that arises during early embryogenesis.

Driver mutation: mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.

Frameshift variant: is a type of mutation caused by the insertion or deletion of a number of nucleotides that is not divisible by three in a nucleic acid sequence. Because of the triplet nature by which nucleotides code for amino acids, a mutation of this sort causes a shift in the reading frame of the nucleotide sequence, resulting in the sequence of codons downstream of the mutation site being completely different from the original. Frameshift mutation often lead to a premature stop codon and therefore loss of function.

Gene: is the basic physical and functional unit of hereditary information that occupies a fixed position (locus) on a chromosome. Genes used to be defined as stretches of DNA that contain instructions that are copied into RNA and then turned into proteins.

Genotype (from the Greek *genos*, meaning race, offspring): The complement of alleles present in a particular individual's genome that give rise to the individual's phenotype.

Genotype-phenotype correlations: a statistical relationship that predicts a physical trait in a person or abnormality in a patient (phenotype) with a given mutation or a group of similar mutations (genotype).

Germline mutation: a heritable change in the DNA that occurred in a germ cell (a cell destined to become an egg or in the sperm). Germline mutations can be passed on to future generations.

Heritability / inherited: the transmission of genetic information from a parent to a child.

Heterogeneous: refers to the occurrence of clinically different types of genetic conditions due to mutations in the same gene.

Heterozygous: refers to having inherited different alleles at a particular gene locus from each parent.

Human genome project (HGP): international scientific effort that began in the 1980s to 'read' the order of bases (sequence) as they appear in the DNA of human chromosomes. The objective is to create a directory of the genes that can be used to answer questions such as what specific genes do and how they work.

Imaging techniques of (neuro) endocrine tumors

- Ultrasound is primarily used in thyroid and parathyroid imaging. This technique has the advantages of near-universal availability, intraoperative utility, minimal expense and lack of radiation.
- Computed tomography (CT) is used for disease staging and surgical planning as they provide more anatomic detail of the tumors themselves and surrounding structures.
- Magnetic resonance imaging (MRI) is not a first-choice imaging tool for most endocrine tumor, however might be used to image curtain metastasis.
- ^{18}fluoro-deoxy-glucose PET (FDG PET) is used to detect malignancy for a variety of tumor types, based on metabolic activity.
- ^{123}I-metaiodobenzylguanidine (MIBG) is an analog of norepinephrine that is used to image catecholamine-secreting paragangliomas.
- Somatostatin receptor-based imaging techniques (e.g. OctreoScan (^{111}In-DPTA-D-Phe-1-octreotide) and ^{68}Ga-DOTATATE) are used to detect neuro-endocrine tumors, for staging, follow-up for disease recurrence and to select patients for peptide receptor radionuclide therapy (PRRT).
- ^{99m}Tc-sestamibi scintigraphy is a radiotracer imaging techniques for preoperative location of parathyroid tumors.

Micro RNAs (miRNAs): are a small non-coding RNA molecules that functions in RNA silencing and post-transcriptional regulation of gene expression.

Missense mutation: is a single-nucleotide substitution (e.g., C to T) that results in an amino acid substitution (e.g., histidine to arginine). Also referred to as non-synonymous variant.

Mutually exclusive mutational patterns: refers to the situation that mutations in two different genes do not occur simultaneously or occurs very rarely together in the same patient. Major driving oncogenes are commonly mutually exclusive.

Nonsense mutation: is a single-nucleotide substitution (e.g., C to T) that results in a stop codon. Also referred to as non-synonymous variant.

Oncogene: is a gene that, when activated by mutation, increases the selective growth advantage of the cell in which it resides.

Penetrance: refers the proportion of individuals carrying a particular gene mutation (genotype) that also express an associated disorder (phenotype). Penetrance less than 100%, is referred to as reduced or incomplete penetrance.

Phenotype (from the Greek *phaino-*, from *phainein*, meaning to show): the physical and/or biochemical characteristics of a person, determined by their genotype and/or environment.

Polygenic: condition or characteristic that is caused by many different genes acting together.

Polymorphisms / benign variant: DNA variant that is observed in natural populations and do not cause any harm to the individual. A gene locus is in general defined as polymorphic if a allele has a frequency of 0.01 (1%) or more.

Prediction software: is used to analyze the effect of a gene mutation. Often used is the Alamut software (Interactive Biosoftware, Rouen, France), which incorporates e.g. Align GVGD, SIFT, and PolyPhen2.

- Align GVGD is a web-based program that combines the biophysical characteristics of amino acids and protein multiple sequence alignments.
- SIFT (Sorting Intolerant From Tolerant) predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids.
- PolyPhen-2 (Polymorphism Phenotyping v2) predicts possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations.

Public genomic databases: aggregate and harmonize exome sequencing data from a variety of large-scale sequencing projects as part of various disease-specific and population genetic studies (i.e. Exome aggregation consortium [ExAC], The Cancer Genome Atlas [TCGA], and Genome of the Netherlands [GoNL]).

Predisposition: refers to having genetic factor(s) that may make an individual more likely to develop a particular condition than the general population.

Preimplantation genetic diagnosis (PGD): is an adjunct to the IVF process where the embryo undergoes genetic testing before it is transferred (implanted) into to uterus.

Pre-symptomatic testing: determines if a person, who does not have any symptoms of the condition at the time, has inherited the mutation (present in their family).

Proband: is the person that serves as the starting point for the genetic study of a family, also referred to as index patient.

Pseudogenes: are characterized by a combination of homology to a known gene but loss at least some functionality. High-sequence similarity between pseudogenes and their functional partners poses a challenge for interpretation of sequencing data. Next-generation sequencing reads are usually few hundred bases in length and cannot be accurately aligned to either in the pseudogene or the real gene. Sequencing errors might cause mismapping of the variable pseudogene sequences (not under selective pressure, hence, they accumulate more variations) and interference with the results obtained for the real gene. Due to high degree of sequence similarity, it is difficult to design Sanger sequencing primers that would not cross-react with pseudogene sequences.

Sanger sequencing: is the gold standard for determining the nucleotide sequence of DNA. This method is based on the selective incorporation of chain-terminating dideoxynucleotides by DNA

polymerase during in vitro DNA replication. It is the most widely used method for the detection of single nucleotide variants (SNVs), often in single genes.

Spice site mutation: occur in the small regions of genes that are juxtaposed to the exons and direct exon splicing. Mutations in these regions may lead to retention of large segments of intronic DNA by the mRNA, or to entire exons being spliced out of the mRNA. These changes could result in production of a nonfunctional protein.

Somatic mutation: occur in any non–germ cells such as those that initiate tumorigenesis. Somatic mutations cannot be passed on to future generations.

Syndrome: group of characteristics and/or symptoms that occur together in a recognizable pattern.

Structural genomic variant: includes any genetic variant that alters chromosomal structure, including inversions, translocations, duplications and deletions. Duplications and deletions, collectively known as copy number variation are the most common form of structural variation in the human genome.

Synonymous vs non-synonymous: a synonymous change in the DNA sequence does not result in the change in the amino acid sequence, e.g. GTT>GTC both code for Valine. A nonsynonymous change does results in the coding of a different amino acid e.g. GTT>GAT results in Val>Asp. These nonsynonymous changes include missense, nonsense, frameshift, splice site, and indel mutations.

Tumor suppressor gene: makes a protein that helps control cell growth. Inactivating mutations in tumor suppressor genes increases the selective growth advantage of the cell in which it resides and therefore may lead to cancer.

Variant pathogenicity classification (according Plon et al. 2013): intended to improve the clinical utilization of genetic testing results, to maximize the opportunity to learn more about variants for the benefit of other families and to minimize the risk of incorrect interpretation of variants in the clinical setting.

Class	Description	Probability of being pathogenic	DNA-test / surveillance at-risk asymptomatic relatives	Research Testing of Family Members
5	Pathogenic	>0.99	DNA test and full surveillance	Not indicated
4	Likely Pathogenic	0.95–0.99	DNA test* and full surveillance	May be helpful to further classify variant
3	Uncertain significant (VUS)	0.05–0.949	No DNA test* and surveillance based on family history (and other risk factors)	May be helpful to further classify variant
2	Likely Benign	0.001–0.049	No DNA test* and treat as "no mutation detected" for this disorder	May be helpful to further classify variant
1	Benign	<0.001	No DNA test* and treat as "no mutation detected" for this disorder	Not indicated

*Consider continuing to test probands for any additional testing modalities available for the disorder in question
Table adjusted from Plon et al. Hum Mutat. 2008

Whole exome sequencing: technique for sequencing all of the protein-coding region of genes in a genome (known as the exome). Humans have about 20.000 genes with in total 180.000 exons, constituting about 1% of the human genome.

Whole genome sequencing: process of determining the complete DNA sequence of an organism's genome at a single time, including the protein-coding and non-coding regions. For a human, a whole genome is approximately 3 billion base pairs, haploid—so 6 billion base pairs to capture the whole diploid complement per cell. Non-coding DNA is not part of an active gene that contains a code for making a protein, also referred to as 'junk DNA'. Recent evidence shows that at least some non-coding DNA is involved in biological processes such as regulation of gene expression and chemical signaling among cells.

LIST OF ABBREVIATIONS

ATC	anaplastic thyroid carcinomas
CBME	ciliary body medullo-epithelioma
CMV-PTC	cribriform-morular variant
CN	cystic nephroma
DTC	differentiated thyroid carcinoma
FAP	familiar adenomatous polyposis
FDA	food and drug administration
FFPE	formalin-fixed, paraffin-embedded
FIHP	familiar isolation hyperparathyroidism
FMNTC	familial non-medullary thyroid carcinoma
FMTC	familial medullary thyroid carcinoma
FTC	follicular thyroid carcinoma
FVPTC	follicular variant of PTC
GIST	gastrointestinal stromal tumor
HCC	hürthle cell carcinomas
HE	hematoxylin-and-eosin
HNPGL	head and neck paraganglioma
HPT	hyperparathyroidism
HPT-JT	hyperparathyroidism–jaw tumor
IHC	immunohistochemistry
LOH	loss of heterozygosity
LOVD	leiden open variation database
MAPK	mitogen-activated protein kinase
MEN	multiple endocrine neoplasia
MNG	multi nodular goiter
mTOR	mammalian target of rapamycin
NET	neuroendocrine tumor
NGS	next-generation sequencing
NIFTP	noninvasive follicular thyroid neoplasm with papillary-like nuclear features
NMTC	non-medullary thyroid carcinoma
PA	parathyroid adenoma
PC	parathyroid carcinoma
PDTC	poorly differentiated thyroid carcinoma
PGL	paragangliomas
PHEO	pheochromocytoma
pHPT	primary hyperparathyroidism
PPB	pleuropulmonary blastoma

PTC	papillary thyroid carcinoma
RAI	radioactive iodine
RAI-R	radioactive iodine refractory
RCC	renal cell carcinoma
SDH	succinate dehydrogenase
SLCT	sertoli-leydig cell tumor ovarian
SPGL	sympathetic paraganglioma
TC	thyroid cancer
TCGA	the cancer genome atlas
VUS	variant of uncertain significance
WES	whole exome sequencing
WGS	whole genome sequencing

ABOUT THE AUTHOR

Karin van der Tuin was born on September 19th 1987 in Groningen, the Netherlands. In 2005 she completed athenaeum secondary education at Dr. Aletta Jacobs College in Hoogezand-Sappemeer. In the same year she started her studies Biomedical Sciences at the Leiden University Medical Center (LUMC). In 2007 she started Medical School in parallel to her study Biomedical Sciences at the LUMC. She wrote her Biomedical Sciences undergraduate thesis on patients with diabetes mellitus or hypertension at risk for development of chronic kidney diseases in primary health care setting under supervisor of Prof. F.W Dekker. As a medical student, she worked as student-assistant in (neuro) physiology and epidemiology education at the LUMC. In 2012, she obtained her Bachelor degree in Biomedical Sciences and Medicine. Between 2011-13 she was a member of the Medicine Curriculum Review Task Force at the LUMC. She obtained her Medical Master Degree in 2014 after a senior internship at het Department of Clinical Genetics of the LUMC. Directly followed by a 6 months residency in onco-genetics at the same department. In November 2014 she started working on her PhD project on rare endocrine tumors under supervision of Prof. Hans Morreau and Dr. Frederik Hes, without allocated financing. In February 2017, after three rejected grant proposals, she and her supervisors received in collaboration with Prof. Thera Links from the University Medical Centre Groningen a grant from the Dutch Pediatric Cancer Society (KiKa), for the project titled: "The Genetic Background of Non-Medullary Paediatric Thyroid Carcinoma" to further continue her PhD research. During her PhD period, she orally presented her research at several national and internal conferences and supervised several students during their internships. She participated in multidisciplinary endocrine cancer patients meetings and counseled patients for research projects. Furthermore, she initiated and participated in several societal impact scientific projects besides the PhD and she was an invited speaker at many public events. In February 2019, she started her postgraduate training as a clinical geneticist (residency) under supervision of Dr. Emilia Bijlsma at the LUMC. In the coming years she would like to combine her residency with endocrine cancer genetics research.

PHD PORTFOLIO

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PhD period: November 2014- December 2019

Promotores: Prof. Dr. H. Morreau, Prof. Dr. T.P. Links, Prof. Dr. F.J. Hes

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Education and Courses

General academic skills

Introduction PhD course	2014
Basic course in legislation and organization for clinical researchers (BROK®)	2016
Basic methods and reasoning in Biostatistics (1.5 ECTS, mark 9)	2017

Research skills

Courses in the program of the Boerhaave Continuing Medical Education, Leiden University Medical Center or Graduate school Medical Genetics Centre South-West Netherlands

Introduction genetic epidemiology	2014
MGC Next Generation sequencing (1.4 ECTS)	2016
MCG Genome Maintenance and Cancer (0.8 ECTS)	2016
Practical Linux (0.4 ECTS)	2017
Introduction in Shark	2017

Other courses in the program of the Leiden University

Writing for a broader audience	2017
Social media	2017
Writing grand proposal	2018

(Inter) national conferences

Annual International Society of Pediatric Oncology (SIOP) Meeting, Cape town, South-Africa (attendance)	2015
Annual Young Dutch Endocrine Meeting, Leiden, the Netherlands (2x oral presentation)	2015
Annual American Thyroid Association Meeting, Victoria, Canada (poster presentation)	2017
Joint meeting UK / Dutch Clinical Genetics Societies & Cancer Genetics Groups, Utrecht, the Netherlands (oral and poster presentation).	2018
Annual RD-connect meeting, Athens, Greece (poster presentation)	2018
Annual American Thyroid Association Meeting, Washington, USA (poster presentation)	2018
Annual International Society of Pediatric Oncology (SIOP) Meeting, Lyon, France (poster)	2019

Symposia and Meetings

Weekly seminars department of Pathology and Clinical Genetics, Leiden University Medical Center (several oral presentations)	2014-19
Weekly molecular tumor genetics meeting, Leiden University Medical Center (several oral presentations)	2014-19
Yearly science and education day department of Clinical Genetics, Leiden University Medical Center (several oral presentation)	2014-19
Science and Society meeting ZonMw, Utrecht, the Netherlands (invited speaker).	2017
Introduction day Biomedical Science students, 2018, Leiden, the Netherlands (invited speaker).	2018
Research lunch meeting Biopharmaceutical Science students, 2018, Leiden, the Netherlands (invited speaker).	2018
Adrenal Masterclass, 2019, Amsterdam, the Netherlands (invited speaker).	2019
DNA lab day for biology and chemistry teachers, 2019, Delft, the Netherlands (invited speaker).	2019

Teaching

Hereditary cancer course, Medicine, second year students	2014-19
Critical appraisal of a topic course, Medicine, third year students	2014-19
Student internship projects guidance	2014-19

Public science projects

Lowlands Science

- Thrill-seeking gen (DRD4) [in Dutch] *(zie fragment New Scientist op YouTube)* — 2015
  - [in Dutch] Galileo *(zie fragment op YouTube)*
  - [in Dutch] Klokhuis *(kijk terug via NPO)* — 2017
- DNA dating [in Dutch] *(zie fragment op YouTube)*

Science Battle — 2017-19

Face of Science, Royal Netherlands Academy of Arts and Sciences — 2018-19

- Schildkliekanker bij kinderen [in Dutch] *(zie fragment op YouTube)*

Public lectures

[in Dutch] 'Leve adventure DNA', Cafe Scientifique, Amsterdam	2016
[in Dutch] 'Zit de voorkeur voor hutspot, haring en bier in je genen?', Leiden	2016
[in Dutch] 'Heeft u het in zich om ooit Olympisch goud te winnen?' Wetenschapsdag LUMC, Leiden	2016

'Exploring the genetic background of pediatric thyroid carcinoma using whole genome sequencing' FameLab, Leiden, the Netherlands	2017
[in Dutch] 'Leve Adventure DNA!' Wereld DNA dag, Corpus, Leiden	2017
[in Dutch] 'DNA-daten', Wetenschapsdag LUMC, Leiden	2017
[in Dutch] 'Is DNA daten, het daten van de toekomt?', Nacht van Kunst en Kennis, Leiden	2017
[in Dutch] DNA en Sport; Kun jij olympisch goud winnen?, Corpus, Leiden	2018
'Your DNA in the cloud', TEDx Leiden University, Den-Haag, the Netherlands *(see fragment on YouTube)*	2018
[in Dutch] 'Talkshow van de Toekomst – Voortplanting', Tivoli Vredenburg, Utrecht (zie fragment op YouTube)	2018
[in Dutch] Is DNA daten, het daten van de toekomt?, Expeditie Next Festival, Rotterdam	2019

DANKWOORD

In de laatste woorden van dit proefschrift wil ik graag iedereen die heeft bijgedragen hartelijk bedanken, in het bijzonder de betrokken patiënten en families.

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Prof. Hes, introduceerde mij in het onderzoeksveld van de endocriene tumoren. Beste Frederik, ik heb veel geleerd van jou gestructureerde werk en diplomatieke talent in samenwerken. Ook veel dank voor het verbeteren van mijn stukken, de samenvoegingen en koppelwoorden, ik leer het waarschijnlijk nooit. Merci beaucoup!

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Lieve papa en mama, ik was twee jaar oud toen ik zei 'zelf doen', nu 30 jaar later zeg ik nog steeds 'zelf doen'. Dankzij jullie onvoorwaardelijke vertrouwen, steun en liefde heb ik mijn eigen keuzes en eigen fouten kunnen en mogen maken. Ik ben jullie heel erg dankbaar.