KU LEUVEN

FACULTY OF MEDICINE

# Mutation analysis in cutaneous mastocytosis in children

Master Thesis proposed to achieve the degree of master in medicine by

**Eline VERYSER**

Unit: Faculty of Medicine

Department of Pediatrics

Promotor: Prof. dr. Dominique BULLENS

Leuven, 2018-2019

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**COVER LETTER**

Dear members of the editorial board,

I kindly present to you our paper 'mutation analysis in children with cutaneous mastocytosis: a systematic review' for careful consideration for publication in your journal.

Mastocytosis is a heterogeneous group of disorders and affects approximately 1 in 10 000 subjects. Whereas in children mastocytosis mostly presents as a cutaneous form, adults generally present with systemic mastocytosis. Cutaneous mastocytosis usually regresses spontaneously after puberty, in contrast to lifelong symptoms in adults. A broad range of mutations that play a role in mastocytosis have been identified. Adults typically present with mutations in c-KIT receptor on mast cells leading to chemical activation. This results in abnormal mast cell growth. This abnormal cell growth is the underlying mechanism of disease in mastocytosis. In children, even more mutations have been described, but their role is less well studied. The particular role of specific mutations in children is the subject of current studies.

In this study, we systematically reviewed the current literature in this promising research field in order to give an overview of the identified mutations. Moreover, we discuss the most important implications of several mutations on treatment options and evolution. To realize this, we screened the PubMed database by using a standardized search strategy. After systematically filtering the results, 14 articles were included for the analysis.

We believe that this study contributes to the existing research because knowledge of the different mutations that play a role in mastocytosis could optimize the therapeutic options and could help to identify children at risk to develop systemic mastocytosis. Considering this important implications, I hope you appreciate reading this paper and consider it for publication in your journal.

I declare that this study is original, non-published work and there were no financial or other competing interests.

Yours sincerely,

Eline Veryser

**ABSTRACT**

**Background:** Mastocytosis is a heterogeneous disease that can be limited to the skin (cutaneous mastocytosis) and/or can involve extracutaneous tissue (systemic mastocytosis). Recent studies identified several mutations that play a role in mastocytosis. This mutation analysis is typically relevant in systemic mastocytosis in adults. However, the correlation of mutations with disease activity and clinical presentation in children is poorly characterized. The aim of this study is to give a review of all identified mutations in children with cutaneous mastocytosis and their correlation with clinical presentation in children in order to analysis this risk in developing a systemic type of mastocytosis.

**Methods:** A systematic review was conducted using the PubMed database. Keywords 'child', 'cutaneous mastocytosis' and 'mutation' were searched. Studies including only adult patients or dealing only about systemic mastocytosis were excluded.

**Results:** 14 papers meeting predefined criteria were analysed. 11 mutations were reported to be associated with mastocytosis in childhood. Mutations in children with cutaneous mastocytosis differs substantial from adults with mastocytosis. A few possible correlations between genotype and clinical presentation or disease outcome were carefully made by some authors, however further research is highly recommended.

**Conclusion:** Further research, including large-scale studies in children with mastocytosis is required to improve the treatment for these patients, especially long term prospective studies. Knowledge on specific mutations could be used in clinical practice to better adapt the treatment of pediatric mastocytosis in function of the chance to develop systemic mastocytosis.

## NEDERLANDSTALIGE SAMENVATTING

**Achtergrond:** Mastocytose is een zeer heterogene aandoening die kan gelimiteerd zijn tot de huid (cutane mastocytose) en/of zich kan uitbreiden naar extracutane weefsels (systemische mastocytose). Recente studies hebben verschillende genen geïdentificeerd die een rol spelen in mastocytose. Deze mutatie-analyse is voornamelijk uitgevoerd bij volwassenen met systemische mastocytose. De correlatie van deze mutaties met ziekteactiviteit en kliniek bij kinderen is echter zeer beperkt beschreven. Het doel van deze studie is het oplijsten van al deze genen bij kinderen met cutane mastocytose en hun correlatie met de klinische presentatie en het risico op het ontwikkelen van een systemische vorm van mastocytose.

**Methoden:** De PubMed database werd gescreend aan de hand van volgende zoektermen: 'child', 'cutaneous mastocytosis' en 'mutation'. Studies die enkel mastocytose bij volwassenen of systemische mastocytose bespraken, werden geëxcludeerd.

**Resultaten:** 14 artikels die voldeden aan vooraf opgestelde criteria werden geanalyseerd. In totaal bleken 11 mutaties gecorreleerd te zijn met mastocytosis bij kinderen. Mutaties in kinderen met cutane mastocytose verschillen substantieel van die beschreven bij volwassenen met mastocytose. Een aantal correlaties tussen genotype en klinische presentatie of ziekteverloop werden met voorzorg gemaakt door sommige auteurs, verder onderzoek is echter noodzakelijk.

**Besluit:** Verder onderzoek, met inbegrip met grootschalige studies bij kinderen met mastocytose is nodig om de behandeling voor deze patiënten te verbeteren. Er is vooral nood aan prospectieve lange termijn studies. Een betere kennis over specifieke mutaties zal in de klinische praktijk bruikbaar zijn om de behandeling van cutane mastocytose bij kinderen beter aan te passen in functie van de kans om systemische mastocytose te ontwikkelen.

## INTRODUCTION

Cutaneous mastocytosis (CM) is a disease characterized by an increased number of mast cells (MCs) in the skin. When also extracutaneous tissue is involved, the disease is called systemic mastocytosis (SM). Mastocytosis is an orphan disease with unknown prevalence.[1,2,3] Based on the classification of the World Health Organisation, cutaneous mastocytosis can be divided into different subtypes: maculopapular CM, also named urticarial pigmentosa (UP), diffuse cutaneous mastocytosis (DCM) and localized mastocytoma of skin (**Table 1**).[1] Of these three variants, the most common type is UP and is present in 65% of all pediatric cases.[2]

Systemic mastocytosis describes forms of mastocytosis in which multiple extracutaneous organs are involved. Systemic mastocytosis can be divided in five subcategories based on the 2016 WHO diagnostic criteria: indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), SM with an associated hematologic neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukaemia (MCL) (**Table 1**).[1] Adults who develop mastocytosis more often have systemic forms.[2] SM is unusual in children. Nevertheless, there is a grey zone between CM and SM: for example a nonspecific presentation of mastocytosis is associated with gastrointestinal symptoms such as diarrhoea, vomiting and nausea. This subtype can be seen as a variant of CM because of the almost impermeable gastrointestinal barrier or it can be classified as SM because of the involvement of extracutaneous tissue.

Table 1: WHO classification of mastocytosis 2016[1]

| |
|---|
| **Cutaneous mastocytosis** |
| Maculopapular cutaneous mastocytosis = Urticaria pigmentosa |
| Diffuse cutaneous mastocytosis |
| Localized mastocytoma of the skin |
| **Systemic mastocytosis** |
| Indolent systemic mastocytosis |
| Smoldering systemic mastocytosis |
| Systemic mastocytosis with associated hematologic neoplasm |
| Aggressive systemic mastocytosis |
| Mast cell leukemia |

CM usually develops in childhood and the prognosis is good: most improve or resolve completely by adolescence.[1,4] Resolution rate varied depending on the mastocytosis subtype. There is a tendency for spontaneous resolution before puberty in children with CM, however 15-30% of children whose disease persists into adulthood will develop internal involvement.[5] Complete resolution is observed in UP and cutaneous mastocytoma: the complete resolution rate for urticarial pigmentosa is approximately 2% per year and for cutaneous mastocytoma 10% per year.[2] Given the extensive involvement of DCM and subtypes of SM, it is not surprising that complete resolution was not demonstrated for these mastocytosis subtypes. Generally, in children with cutaneous mastocytosis in about 67-90% of patients, a total disappearance of the lesions or marked improvement can be observed.[4,6] Although paediatric mastocytosis is a benign and spontaneously regressing disease, it is impossible to predict the evolution in advance.[4] In a particular part in children with the cutaneous form of mastocytosis, the disease will persist and will sometimes develop into internal involvement.[5] It is still not known which children will convert into a systemic form of mastocytosis. One of the potential benefits of mutation analysis could be that some of the observed mutations could predict which

children seem to persist or to develop a systemic form of mastocytosis and which part of children will spontaneously resolve.[6]

CM is diagnosed clinically and combined with laboratory tests. Darier's sign is often used as a diagnostic marker: the appearance of a swelling, after gentle rubbing a cutaneous mastocytosis lesion (**Figure 1**).[7] It is highly specific for mastocytosis.[4,5,8] It is pathognomonic for the presence of mast cells within the lesion. In about 50% of cases, the diagnosis can be based only on clinical examination including a positive Darier's sign.[2,9] However the diagnosis must be confirmed by biopsy and histology if the skin lesion is uncertain in nature.[10] In CM, the biopsy of lesional skin reveals MC infiltration, sometimes with atypical MCs forming aggregates in local areas.[11]

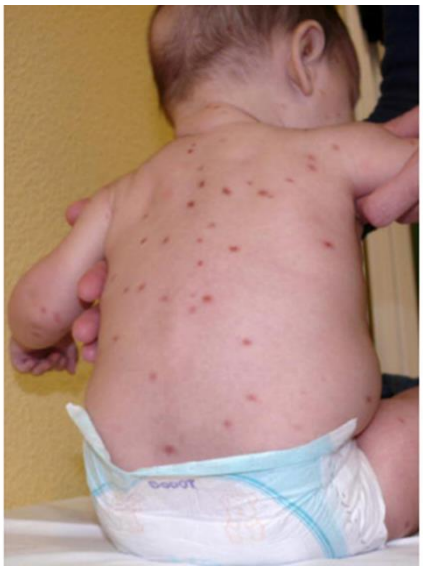
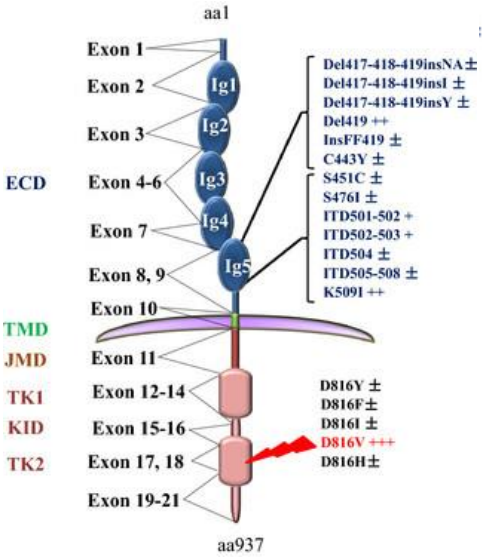


**Figure 1: Urticaria pigmentosa** (5)

Once the diagnosis is clear, a treatment plan should be made. At this time, the most important treatment modality consists of avoiding triggers for mast cell degranulation. Triggers may include foods, insect stings, general anesthetics, physical stimuli, changes in temperature, anxiety, medications, and exercise.[3,7] In the hospital of the university of Leuven, guidelines exist for the use of local and general anesthetics (**Supplemental document 1**). In the preoperative setting, specific measures should be taken.[12] Causal treatment is not yet available. Pharmacologic treatment includes antihistamines: both H1 and H2 antihistamines are useful. Antileukotriene drugs (eg, montelukast) may be added in patients that are not optimally controlled by antihistamines. Furthermore, all caretakers should carry an epinephrine autoinjector at all times.[3,13]

Adult mastocytosis is frequently associated with specific mutations. It is a clonal disease frequently associated with activating c-KIT mutations that causes abnormal mast cell accumulation and activation.[14,15] Recent studies have demonstrated that also in paediatric mastocytosis a high frequency of mutations are present.[16] Skin biopsy may be submitted for mutational analysis of KIT. Identifying potential genes that play a role in the development of mastocytosis is subject of current clinical trials. Factors that predict the course and severity of mastocytosis in children have not been completely identified.

Structure of a normal KIT (KIT WT) is represented in **Figure 2**.




KIT is a type III receptor tyrosine kinase; binding of its ligand stem cell factor (SCF) leads to receptor dimerization and activation. Activating mutations in KIT result in ligand-independent receptor dimerization and autophosphorylation, leading to alterations in apoptosis, cell proliferation and differentiation.[16] The KIT gene, located on chromosome 4q12, contains 21 exons translated into a transmembrane receptor tyrosine kinase (RTK). KIT structure is characterized by an extracellular domain (ECD), a transmembrane domain (TMD) and a cytoplasmic region. The cytoplasmic region of KIT consists of an autoinhibitory juxtamembrane domain (JMD) and a kinase domain, including a large kinase insert domain (KID) (7). The KIT gene contains 21 exons. The five immunoglobulin-like loops of the ECD are encoded by exons 1-9 (amino acid residues 23-520), the TMD by exon 10 (amino acid residues 521-543), the JMD by exon 11 (amino acids 544-581) and the TK domain is encoded by exons 13-21 (amino acids 582-937).[18]

**Figure 2: structure of normal KIT**
Abbreviations: ECD, extracellular domain; TMD, transmembrane domain; JMD, juxtamembrane domain; KID, kinase insert domain; TK, tyrosine kinase. Derived from: https://www.researchgate.net/figure/Structure-of-the-KIT-receptor-and-positions-of-the-major-mutations-found-in-mastocytosis_fig1_273386447.[17]

The relevance of mutations in c-KIT or in other proteins in childhood mastocytosis is less clear. The purpose of this study is to give a review of the mutations currently linked to cutaneous mastocytosis in children and to determine if they can be used as a predictor for disease activity and clinical presentation. Moreover, we discuss what the clinical implications of several mutations are and define whether or not if it is useful to perform genetic tests in children with mastocytosis. In connection, we discuss potential specific treatment options based on genetic mutations in CM. A special focus will be given to the question if particular mutations can predict if childhood CM is likely to convert into SM and/or might indicate childhood SM instead of CM. If we could predict which children are suspect to develop a SM in life, we could potentially start earlier with more effective treatment and reduce the chance that mastocytosis will deteriorate in a systemic form.

## METHODS

This report was written using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed database was screened using the following search algorithm: "child"[MeSH Terms] AND "mastocytosis, cutaneous"[MeSH Terms] AND "mutation"[MeSH Terms]. No additional filters were applied. Articles were selected on Mesh terms, scientific relevance and quality. Because of the limited extent of articles about this topic, ‘quality’ was considered sufficient if the methods section was clearly explained and logical in structure. No other quality filters were applied.

## RESULTS

The literature search strategy is summarized in the flow chart presented in **Figure 3**. After removal of duplicates, selection was conducted at three levels. The first selection was based on screening of the titles. 3 titles were eliminated: one study because it was not applicable to the key question of this review, namely "mutation analysis in cutaneous mastocytosis", one study was only dealing with systemic mastocytosis and one study was conducted in adult patients only. Next, selected titles were reviewed by abstract. Five studies were removed. Reasons for removal were: one article was not written in English but in Spanish, the full text of one article was not available, one article was not about cutaneous mastocytosis (but about multifocal capillary malformations), one study was a case study about UP but without mutation analysis, and one study was not clinically oriented but was talking about the processes of detection of c-KIT mutations. This stepwise process resulted in 12 remaining studies for full-text screening. At this third level, two studies were excluded, one since full text was not related to defined outcomes of interest, namely cutaneous mastocytosis in children, but mainly about the role of molecular genetics in mastocytosis in adults. The second article was a review article with no distinction between adults and children and without discussing mutation analysis. In the end, 4 articles were supplemented after a process of snowballing in the references of selected articles.

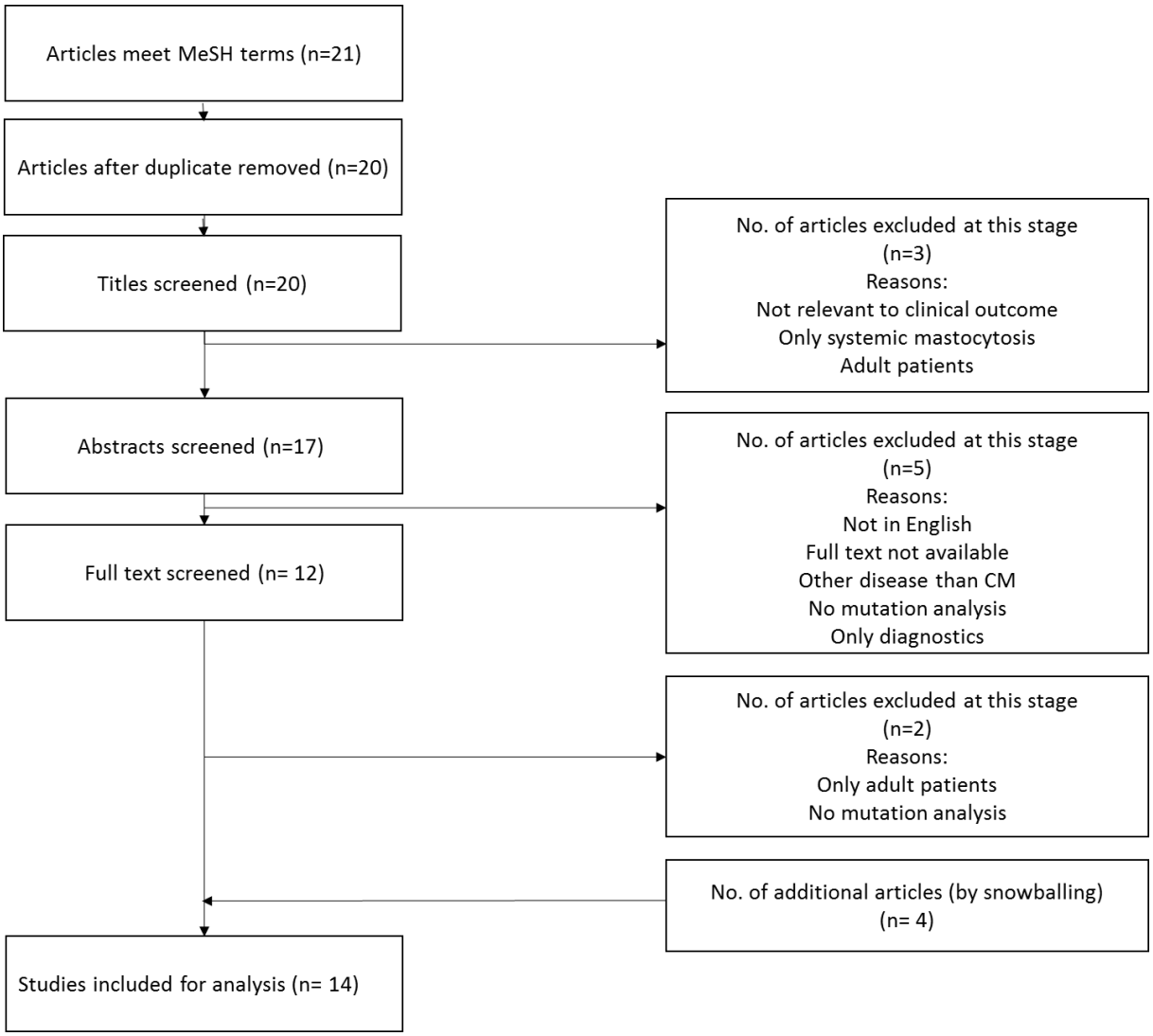



**Figure 3: Flow diagram showing search results in PubMed.**

Finally, a total of 14 studies were included in our review. **Table 2** represents the characteristics of the included studies.

**Table 2: Included articles**

| | Study | population | N children included | Tissue analysed | Major mutations |
|---|---|---|---|---|---|
| 1. | Chan et al. (2018) | Cutaneous mastocytosis | 9 children (+ 43 adults) | Skin | D816V<br>D816Y<br>V560G<br>M541L<br>ITD502-503<br>WT |
| 2. | Pollard et al. (2015) | familial mastocytosis | 3 siblings | Blood | R634W |
| 3. | Méni et al. (2015) | Childhood mastocytosis | 215 children | Bone marrow/blood | D816V<br><>exon17*<br>WT |
| 4. | Ma et al. (2014) | Childhood mastocytoma | 9 cases | Skin | D816V<br>ITD502-503<br>WT |
| 5. | Fett NM et al. (2013) | Familial UP | 3 family members | Skin | WT |
| 6. | Wöhrl et al. (2012) | Familial mastocytosis | 4 family members | Skin | S849I |
| 7. | Bodemer et al. (2010) | Pediatric mastocytosis | 50 children | Skin | D816V<br>D816_<br>Del 419<br>ITD 502-503<br>K509L<br>WT |
| 8. | Hoffmann et al. (2008) | Childhood CM | 1 case | Skin | Del 419 |
| 9. | Lanternier et al. (2008) | Childhood vs adult onset mastocytosis | 26 childhood onset (+ 114 adult onset) | Skin | D816V<br>DEL419<br>K509L<br>WT |
| 10. | Masserot et al. (2008) | Childhood mastocytosis and ALL | 2 cases | Bone marrow | WT |
| 11. | Verzijl A et al. (2007) | Mastocytosis | 12 children (+ 11 adults) | skin | D816V<br>WT |
| 12. | Yanagihori et al. (2005) | Childhood vs adult onset mastocytosis | 12 childhood onset (+ 4 adult onset) | Skin | D816V<br>D816F<br>WT |
| 13. | Daley t et al. (2001) | Cutaneous mastocytosis | 9 children (+ 4 adults) | Peripheral blood cells | IL4-R-Q576R |
| 14. | Buttner et al. (1998) | Childhood vs adult onset mastocytosis | 11 childhood onset (+ 6 adult onset) | Skin | D816V<br>V560G |

* Del 419, F522C, ITD502-503, K509I, M541L
Abbreviations: UP: urticarial pigmentosa; ALL: acute lymphoblastic leukaemia; DEL: deletion; ITD: internal tandem duplication; WT: wild type, CM: cutaneous mastocytosis.

### 1. Mutations in cutaneous mastocytosis

Several mutations have been reported to play a role in mastocytosis. All these studies provided specific hypotheses about the clinical importance of these genes in the presentation, evolution and treatment of mastocytosis. 2 genes, c-KIT and IL4-R, in which respectively 10 and 1 mutations were described, were reported to be associated with mastocytosis by at least one study. Here, the results of the studies will be presented and we will describe them gene by gene. A summary of mutations associated with cutaneous mastocytosis in childhood is presented in **Table 3**. Pediatric mastocytosis is defined as onset of cutaneous mastocytosis before the age of 18.

About 80% of patients with adult mastocytosis carried the D816V mutation in exon 17, whereas 40% of children with CM have mutations in exons 8-11, which are only rarely observed in adults.[4,19,20]

First, we discuss separately the described mutations and their incidence in children with cutaneous mastocytosis as described in the selected articles.

**Table 3: summary of identified mutations**

| Gene | | Mutation investigated | Frequency in childhood (%) | Reference (year) |
|---|---|---|---|---|
| c-KIT | Exon 8 | DEL419 | 1/1 (100)<br>11/215 (5.12)<br>8/50 (14)<br>2/26 (7.7) | Hoffmann et al. (2008) Méni et al. (2015) Bodemer et al. (2010) Lanternier et al. (2008) |
| | Exon 9 | ITD 502-503 | x/215 **<br>3/9 (33.33)<br>5/50 (10)<br>1/9 (11.11) | Méni et al. (2015)<br>Ma et al. (2014)<br>Bodemer et al. (2010)<br>Chan et al. (2018) |
| | | K509L | x/215**<br>5/50 (10)<br>1/26 (4) | Méni et al. (2015)<br>Bodemer et al. (2010)<br>Lanternier et al. (2008) |
| | | F522C | x/215 ** | Méni et al. (2015) |
| | Exon 10 | M541L | 18/215 (8.37)<br>3/9 (33) | Méni et al. (2015)<br>Chan et al. (2018) |
| | | V560G | 0/9 (0)<br>0/11 (0) | Chan et al. (2018)<br>Buttner et al. (1998) |
| | Exon 13 | R634W | 3/3 (100) | Pollard et al. (2015) |
| | **Exon 17** | **D816V*** | 61/215 (28.4)<br>3/9 (33)<br>18/50 (36)<br>2/12 (17)<br>5/9 (56)<br>11/26 (42)<br>7/12 (58)<br>0/11 (0) | Méni et al. (2015)<br>Ma et al. (2014)<br>Bodemer et al. (2010)<br>Verzijl et al. (2007)<br>Chan et al. (2018)<br>Lanternier et al. (2008)<br>Yanagihori et al. (2005)<br>Buttner et al. (1998) |
| | | D816F | 3/12 (25) | Yanagihori et al. (2008) |
| | Exon 18 | S849I | 2/4 (50) | Wöhrl et al. (2013) |
| | WT | | 2/2 (100)<br>7/50 (14)<br>2/12 (16)<br>10/12 (83,3)<br>12/26 (46)<br>3/3 (100)<br>99/215 (46) | Masserot et al. (2008)<br>Bodemer et al. (2010)<br>Yanagihori et al. (2005)<br>Verzijl et al. (2005)<br>Lanternier et al. (2008)<br>Fett et al. (2013)<br>Méni et al. (2015) |
| IL4-R | | Q576R | 6/9 (66.7) | Daley et al. (2001) |

Abbreviations: WT= wild type c-KIT gene

***Exon 17 D816V** is a typical mutation in adults

** Méni et al. did not distinguish the described mutations in exon 9. They could found mutations in exon 9 in 17 of 215 genetic tested children (8%).

Underneath, we will discuss the described mutations separately and focus on their clinically most important findings. A summary of most interesting clinical findings –the text in italics- is represented in **table 4**, situated at the end of this results section.

***c-KIT Exon 8***

Exon 8 is translated in one of the subunits of the ECD of the c-KIT gene. The somatic deletion of codon 419 in exon 8 (DEL419) has been suggested to affect the function of the KIT receptor and therefore influencing the activation of mast cells.

Hoffmann et al. (2008) demonstrated a DEL419 in exon 8 by performing a mutation analysis in an 2-year-old boy with progressive cutaneous mastocytosis. They reported that this specific mutation is one of the few c-KIT mutations that *clinically responds to imatinib therapy*.[21] Bodemer et al. (2010) found that this deletion occurred in eight cases (14%) of the investigated cutaneous biopsies of fifty affected children. They suggested that *activating mutations in exon 8 are selectively involved in childhood-onset mastocytosis*.[20] Lanternier et al. (2008) found 2 children carrying the DEL419 in exon 8 out of 26 children (7.7%) who had undergone mutation analysis.[19] Méni et al. (2015) found that 18% of the 1747 cases (adults + children) carried mutations outside exon 17. This study mentioned DEL 419 in exon 8 of the c-KIT gene in 11 of 215 tested children, so with a frequency of 5.12%.[4]

***c-KIT exon 9***

Exon 9 is also one of the subunits of the ECD of the c-KIT gene. Similar to the DEL319 mutation in exon 8, mutations in exon 9 are described in children with variable frequency and are *very rarely observed in adults.*[20] Relatively frequently described mutations in children with cutaneous mastocytosis in this exon include: F522C (substitution of cysteine instead of phenylalanine on position 522), ITD 502-503 (internal tandem duplication of six base pairs resulting in a duplication of two amino acids 502-503) and K509L (amino acid leucine instead of lysine). These are all activating mutations that cause mast cells to proliferate.

Méni et al. (2015) who perfomed a systematic review on 1747 cases of childhood mastocytosis and performed genetic testing in 215 children, found that possible mutations ITD 502-503, F522C or K509L in exon 9 had a frequency of 17 out of 215 tested patients (7.91%). They did not distinguish between these 3 described mutations, so we do not know the exact frequency of every single mutation.[4] Ma's group (2014) only studied ITD502-503 in exon 9. They found KIT mutations in two-thirds of examined cases (six of nine). In three cases (33%) ITD502-503 was found.[16] They remarked that this same duplication in exon 9 has been reported in 10% of GIST (gastrointestinal stromal tumours) and in small bowel tumours and is *responsive to tyrosine-kinase-inhibitors*. Bodemer et al. (2010) reported the same ITD502-503 and K509L in exon 9. Half of the mutations (22 of 50 patients) they found, were located at exons 8 and 9. Focusing on exon 9, they found ITD 502-503 in 5 out of 50 children (10%) and K509L also in 5 children (10%).[20] Chan et al. (2018) found 1 child out of 9 tested children (11%) with ITD502-503 mutation in exon 9.[14] This study also investigated adults with mastocytosis. 2 adults are positive for ITD502-503 in exon 9, in coexpression of M541L on exon 10. Lanternier et al. (2008) performed a mutation analysis in 26 children with cutaneous mastocytosis. They found only 1 child (4%) carrying a mutation in exon 9: K509L.[19]

***c-KIT exon 10***

The TMD of the c-KIT gene is encoded by exon 10. Mutations in this exon that have been described are M541L and V560G.

Méni's group (2015) reported 18 pediatric cases with M541L mutation in exon 10 (8.37%) out of 512 genetically tested children.[4] Chan et al. (2018) perfomed mutation analysis for mutations in exon 10: they found no V560G mutation in 9 children with mastocytosis (0%), but it was detected in six out of 43 adults. Another mutation in exon 10, M541L, was detected in 3 children out of 9 (33%) and in 8 out of 43 adults with mastocytosis. They could not find a correlation between M541L and symptoms or disease course.[14] Büttner et al. (1998) could demonstrate the mutation V560G in 2 out of 6 adult patients, but in none of the 11 children with mastocytosis.[22]

***c-KIT exon 13***

Exon 13 of the c-KIT gene is part of the exons that codes for the TK domain.

Only one study reported mutations in exon 13. Pollard et al. (2015) reported a novel c-KIT mutation in exon 13: R634W in a familial form affecting three siblings with urticarial pigmentosa. This article is the first one describing R634W mutations in association with mastocytosis. R634W mutations have been previously described in other diseases (mucosal melanoma, chronic myelomonocytic leukemia and acute myeloid leukemia).[23]

***c-KIT Exon 17***

The adult-form of the disease is associated with c-KIT mutations, mostly in exon 17, the D816V mutation (aspartate substitution for valine aminoacid). Exon 17 is situated in the TK domain of the c-KIT gene. Several studies found different frequencies of c-KIT mutations on exon 17 in patients with childhood-onset mastocytosis. In our systematic review, a main aim is to determine whether this particular mutation is also frequent in children and why the clinical extent is so different compared to mastocytosis in adults.

For this reason, Bodemer et al. (2010) examined the skin biopsies of 50 children with cutaneous mastocytosis for mutations in codon 816 (exon 17) and other c-KIT mutations. They reported that a mutation of codon 816 (exon 17) was found in 42% of cases (18 out of 50 children), including 36% the D816V polymorphism, and that mutations outside exon 17 were observed in 44%. Other mutations described in exon 17 were D816Y mutation in 4% of children and a previously undescribed D816I mutation in one patient (2%). Most children with the D816V mutation had urticarial pigmentosa (45%).[20] Similar findings have been reported by Verzijl et al. (2007) in a case study of 12 children with cutaneous mastocytosis. In this study the c-KIT mutation on codon 816 could be demonstrated in 2 out of 12 children (17%).[24] In a more recent study, Méni et al. (2015) investigated the relationship between paediatric mastocytosis and mutations in c-KIT. They found that the KIT D816V mutation was detected in 61 of the 215 genetic tested children (28.4%). *A correlation between KIT mutation and disease outcome was not clearly established*.[4]
Comparable results have been reported by Chan et al. (2018) in an original article with 43 adults and 9 children. KIT-D816V was identified in 5 out of 9 children (56%).[14]
Ma et al. (2014) examined 9 children with solitary mastocytoma, a subtype of cutaneous mastocytosis. They analysed exon 8, 9, 11, 13 and 17 of the c-KIT gene. In six of nine children they found a c-KIT mutation, three of these 6 children had the D816V mutation (33%). They remarked that in contrast to previous studies suggesting that childhood-onset disease lacked c-KIT mutations, pediatric mastocytosis is probably also a clonal disease. But despite clonality, it is mostly self-limited.[16]
A study by Lanternier et al. (2008) performed genetic testing on skin biopsies of 26 childhood-onset and of 114 adult-onset mastocytosis. C-KIT exons 8 to 13 and 17 have been tested. 11 childhood-onset patients (42%) had a D816V mutation. In the adult-onset group 77% carried the D816V mutation. So

patients with an adult-onset form carry more often the D816V mutation than patients with a childhood-onset form. They suggested that *the D816V mutation in pediatric patients may be associated to a higher persistence rate in adulthood.* Furthermore, they found *no evidence for association between genotype and mastocytosis form*. [19]

Yanagihori et al. (2005) found that of 12 patients with childhood-onset mastocytosis, 7 carried the D816V mutation (58%). The mutation analysis also revealed another mutation in exon 17, D816F, in which an aspartate substitutes a phenylalanine. This D816F mutation was found in 3 out of 12 patients with childhood-onset disease (25%). Further research on the epidemiological outcomes showed that *children carrying the D816F mutation develop CM at an earlier age than children carrying the D816V mutation (mean age of onset 1.3 vs 5.9 months).* These findings suggest the relevance of the D816F mutation in the early onset mastocytosis. In this study they did not find any mutations outside exon 17, so *the investigators propose in clinical practice to perform an initial screening of codon 816 in any child presenting with CM.*[17]

In contrast, Büttner et al. (1998) could not find a codon 816 mutation in any of the 11 patients with childhood-onset mastocytosis (0%), but in all 6 samples of patients with adult-onset mastocytosis.[22]

***c-KIT exon 18***

The TK domain of the c-KIT gene is partly encoded by exon 18.

In our systematic review we found one single study that described a mutation in exon 18. Wöhrl et al. (2013) described a previously unreported mutation: ATT instead of AGT at position 849 in exon 18 (S849I). In their study they presented a single family of 8 members with a history suggestive for allergy, including 4 members with cutaneous mastocytosis (positive Darier's sign). Performing PCR analysis on skin biopsies of the c-KIT gene showed a S849I mutation in only 2 affected members (50%), questioning the relevance of this mutation for this presentation.[25]

***IL4- receptor***

Several mutations in the c-KIT gene have been described to play a role in the development of mastocytosis. So far, the genotype cannot predict the clinical phenotype: the presence of c-KIT mutations alone is not sufficient to explain the different clinical forms of the disease. Therefore other mutations are likely to influence the clinical outcome of mastocytosis. In our systematic review, we only found one article handling other mutations than mutations in the c-KIT gene.

Daley et al. (2001) found a mutation in the gene encoding for the receptor for interleukin 4 (IL-4R). IL-4 plays a role in the induction of apoptosis in human mast cells. The hypothesis was considered that *patients carrying the gain-of-function polymorphism Q576R might be relatively resistant to the gain-of-function mutation in c-KIT*. In their study, 36 patients with either cutaneous or systemic mastocytosis were studied for association with the Q576R polymorphism. We focused on the 9 children with cutaneous mastocytosis who were included in the analysis. In this particular group 6 children carried the IL4-R Q576R polymorphism (66.7%).[26]

***Wild type c-KIT gene***

Although in a large proportion of children with cutaneous mastocytosis, a mutation in the c-KIT gene can be found, not all children are carriers of detected mutations. A part that may not be neglected are the children that have undergone mutation analysis, but where no mutations could have been found.

Masserot et al. (2008) conducted a mutation analysis in two children with urticarial pigmentosa who developed B-cell acute lympyhoblastic leukemia (ALL). They analysed exons 8 to 11 and exons 17-19, but no mutations were found. These two children had a WT c-KIT gene.[27] A systematic review by Méni et al. (2015) found that *46% of 215 genetic tested children (99/215) carried none of the mutations that were tested*.[4] A study by Bodemer et al. (2010) found that 86% of children with cutaneous mastocytosis had mutations in c-KIT. So in only 14% of children (7/50) none mutation was found.[20] Verzijl et al. (2007) did a mutation analysis in 12 children with cutaneous mastocytosis. They could find a mutation in the c-KIT gene in only 2 children, so *10 out of 12 (83.3%) have a wild type c-KIT gene*. This high incidence of WT c-KIT gene is in contrast to the high prevalence of mutations that were found in our selected articles. In the discussion of this article, Verzijl searched for a possible explanation for this discrepancy: it may due to insufficient sensitivity of their assay, a different study population or differences in sampling.[24] In a study by Lanternier et al. (2008) 12 out of 26 (46%) children with cutaneous mastocytosis do have a wild type c-KIT gene.[19] Yanagihori et al. (2005) did a DNA analysis in 12 children with cutaneous mastocytosis. 2 of the 12 patients (16.7%) had none mutation in the c-KIT gene.[17] Fett et al. (2013) presented 3 cases of urticarial pigmentosa within one family. Sequencing for KIT exons 8, 10, 11 and 17 was negative for known c-KIT mutations.[28]

**2. Familial mastocytosis**

Most cases of mastocytosis occur as isolated events. Inherited forms of mastocytosis are rare, with fewer than 100 cases reported in the literature.[23] Most commonly urticarial pigmentosa occurs in familial cases, but all subtypes have been reported in familial cases. The etiology of familial mastocytosis is likely a germline mutation in the c-KIT proto-oncogene.[28]

Four studies examined the role of mutations in familial mastocytosis. In a study by Fett et al. (2013) 3 family members with cutaneous mastocytosis were evaluated for KIT mutations. Sequencing of KIT exons 8, 10, 11 and 17 was negative. These data suggest that other mutations in the c-KIT gene or mutations in other genes may cause familial cutaneous mastocytosis.[28] Conflicting results have been reported in other studies on familial mastocytosis. The study, cited earlier, by Pollard et al. (2015) reported a novel familial mastocytosis-related c-KIT mutation (R634W) on exon 13 in three siblings. This R634W has been described in other disease, but not earlier in mastocytsosis.[23] Wöhrl et al. (2012) observed a previously unreported mutation in exon 18 (S849I) in 8 family members. By analysing the clinical symptoms, they remarked that the c-KIT S849I mutation contributes to a rather benign form of CM.[25] In the study already discussed earlier in this systematic review, Bodemer et al. (2010) found that 2 out of 4 children with familial mastocytosis had mutations in exon 17. They concluded that familial childhood-onset mastocytosis can occur with and without mutations in the c-KIT gene.[20]

**Table 4: Clinical features of included articles**

| | Study | Mutations described | Clinical features |
|---|---|---|---|
| 1. | Chan et al. (2018) | D816V<br>D816Y<br>V560G<br>M541L<br>ITD502-503<br>WT | - V560G mutation on exon 10 is associated with more advanced disease |
| 2. | Pollard et al. (2015) | R634W | - benefit of screening for mutation in exon 13 doubtful |
| 3. | Méni et al. (2015) | D816V<br>DEL419<br>F522C<br>ITD502-503<br>K509I<br>M541L<br>WT | *- no clear correlation between D816V mutation on exon 17 and disease outcome*<br>*- half of children with CM carried a WT c-KIT gene* |
| 4. | Ma et al. (2014) | D816V<br>ITD 502-503<br>WT | - interaction of genes causes CM<br>*- ITD 502-503 on exon 9 is responsive to TKI* |
| 5. | Fett NM et al. (2013) | WT | |
| 6. | Wöhrl et al. (2013) | S849I | S849I: tendency to incomplete resolution |
| 7. | Bodemer et al. (2010) | D816V<br>D816_<br>DEL419<br>ITD502-503<br>K509I<br>WT | - combination of c-KIT and other genes<br>*- mutations in exons 8 and 9 frequent in children, rare in adults*<br>- no clear genotype-phenotype correlation<br>- CM in children is a clonal disease |
| 8. | Hoffmann et al. (2008) | DEL419 | *- DEL419 mutation on exon 8 responds to imatinib therapy* |
| 9. | Lanternier et al. (2008) | D816V<br>DEL419<br>K509L<br>WT | *- no association found between genotype – mastocytosis subtype*<br>*- D816V-mutation on exon 17 may be associated with longer persistance* |
| 10. | Masserot et al. (2008) | WT | |
| 11. | Verzijl A et al. (2007) | D816V<br>WT | - D816V is not a germ cell mutation<br>*- 10 out of 12 children have a WT c-KIT gene* |
| 12. | Yanagihori et al. (2005) | D816V<br>D816F<br>WT | *- D816F is associated with younger age of onset*<br>*- They propose to perform a genetic screening of codon 816 in any child presenting with CM* |
| 13. | Daley t et al. (2001) | IL4-R Q576R | *- IL4-R polymorphism has a protective role* |
| 14. | Buttner et al. (1998) | D816V<br>V560G | - Childhood-onset mastocytosis seen as a reactive process rather than a clonal disease. |

This table summarizes the findings on the genes associated with particular clinically important features and the method of sampling tissue analysed for genetic testing.
Abbreviations: CM, cutaneous mastocytosis; TKI, tyrosine-kinase inhibitor; WT, wild-type

## DISCUSSION

The aim of this systematic review was to summarize literature findings on the role of mutations in cutaneous mastocytosis in children and to determine if any marker or mutation can be used as a predictor for disease activity and clinical presentation. Results of our study indicate that several mutations may be involved in the development of cutaneous mastocytosis in children, especially mutations in the c-KIT gene. However, considering the poor number of studies in this research area and the fact that most studies are conducted in adults, it is not easy to draw definite conclusions. Thus, results in this review should be very carefully interpreted.

### 1. Summary of described mutations and their role in cutaneous mastocytosis in children

Here, the results of the studies will be discussed. For a summary of significant clinical findings we refer to the results represented in **table 4** in the results section of this article above. **Figure 4** represents the prevalence of the tested mutations found in our systematic review. In total, in the 14 studies included in our systematic review, 366 single children had undergone mutation analysis. In 344 of children, exon 17 mutations were tested and in 320 of children, WT c-KIT genes were tested. The other mutation analyses were conducted in a smaller part of children. We are aware of the potential referral bias due to the small number of study subjects and the fact that some studies are conducted in smaller health centres. Furthermore, because of concluding systematic reviews as well as original articles, there is a possibility that some children have been included in several of the included studies in our systematic review. Overall, we must be aware of interpreting these results with care.

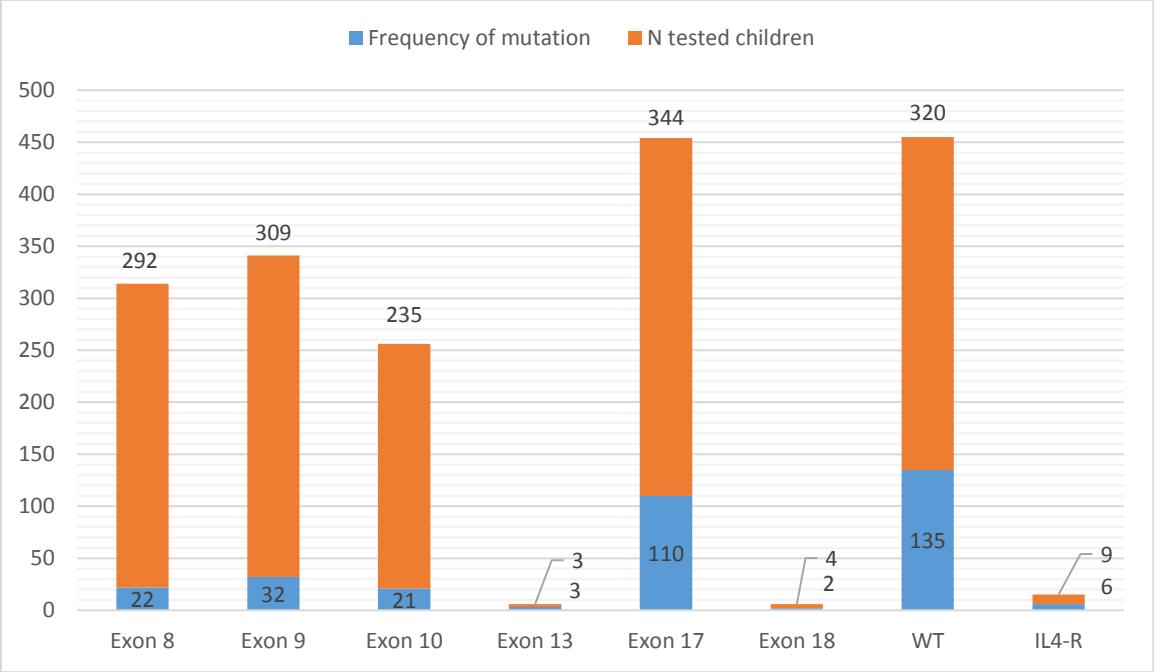



**Figure 4: prevalence of tested mutation in systematic review**
Abbreviations: WT= wild type c-KIT gene; N= number

While in adults, 80% of mastocytosis is associated with the D816V mutation in exon 17, in children a broader range of potential mutations have been described.

Mutations at codon 816 in exon 17 were detected in 110 of a total of 344 children (**32%**) in the 8 studies included in our review that investigated this particular mutation. If we compare this to studies mainly focusing on adults with mastocytosis, this mutation has a much higher incidence in this population, around 80%.[4,14,16,17,19,20,22,24] We can conclude that the D816V mutation is rather uncommon in children with cutaneous mastocytosis. Nevertheless we were unable to correlate the presence of this mutation with clinical presentation or disease outcome. An interesting remark has been made by Ma et al.: they wonder if, although the same mutations in children and adults occur, the impact of this KIT mutation is very different. While in adults the disease is life-long, in children the disease usually regresses spontaneously. They suggested that one possible explanation is that the oncogenic effect of the KIT-mutation is suppressed by the overexpression of other genes.[16] It is a very interesting hypothesis that the interaction of different genes in children could explain the different course of mastocytosis. To prove this, further research is recommended. Bodemer et al. could not find a significant association between the most common mutation in adults (D816V) and disease outcome in children with

cutaneous mastocytosis. They concluded that both adult-onset mastocytosis and childhood-onset mastocytosis are clonal diseases, but the role of specific mutations is not yet clear.[20]
Verzijl et al. found the D816V mutation in 2 out of 12 genetic tested children. These 2 children had urticaria pigmentosa, including one child also showing juvenile xanthogranuloma, consistent with an abnormal clinical presentation. Interesting in this study is that one of the children with the D816V mutation has a monozygotic twin sister without the mutation, confirming that this mutation did not occur early in development and so is not a germ cell mutation.[24]
Another described mutation in exon 17, D816F (substitution from aspartate to phenylalanine at codon 816), was detected in only one study. Indeed, because of the limited data on this mutation, we must be aware of drawing conclusions. Yanagihori et al. found in their study that a relatively higher percentage of patients with childhood-onset mastocytosis carried this mutation as compared to previous reports. They explained this discrepancy as they used different procedures in DNA analysis. In their study the D816F mutation was found at earlier age as compared to the D816V mutation.[17]
An important remark that should be made is that there is a very broad range in prevalence of this D816V mutation. In the study by Büttner et al. the frequency in children is 0%.[22] In contrast, Yanagihori et al. could found this mutation in 58% of genetic tested children.[17] Both studies have a rather low sample size, so we should be careful not to draw conclusions of the exact frequency of this mutation in children, and larger studies are required.

Another mutation frequently described was the DEL419 mutation in exon 8. We could find this mutation in 22 out of a total of 292 children (**7.5%**) in which this mutation was tested.[4,19,20,21] A review by Orfao et al. (2007) found that the frequency of this specific deletion was less than 5%, suggesting that it is a very rare mutation.[18] However, a few other studies analysed in our systematic review found this mutation in mastocytosis in children at much higher incidence. Nevertheless, because the very limited number of patients expressing the DEL419 mutation included in our review, further research on this particular mutation is necessary. The influence of this mutation on clinical outcome of mastocytosis is still a matter of debate. Hoffmann et al. mentioned that this is a known mutation responding to imatinib therapy.[21] Imatinib is a selective tyrosine kinase inhibitor with activity against wild-type KIT and in patients with deletion of codon 419 in exon 8 in pediatric cutaneous mastocytosis.[15] Given this fact, it opens opportunities in the selection of therapy, because this guides the selection of specific tyrosine kinase inhibitors (TKI).

Besides exon 8, exon 9 also encodes for the fifth Ig loop of c-KIT's extracellular domain. In our systematic review in total 309 children were tested for a mutation in exon 9 of the c-KIT gene. 32 children were found carrying a mutation in this exon (**10.4%**).[4,14,16,19,20] In a study by Bodemer et al. almost 50% of the mutations outside exon 17 were located in these two genes. Interesting, they could not find a clear phenotype-genotype correlation in the patients carrying mutations in exon 8, 9 or 11. Furthermore, none child with familial mastocytosis had mutations in exons 8, 9 or 11.[20] According to these results, it seems that there are several hot spots for mutations in childhood-onset mastocytosis at exons 8 and 9.

Several remarks should be made while discussing mutations in exon 10. Chan et al. could not find a V560G mutation in any of the genetically tested children, but this particular mutation was detected in 6 out of 43 adults. Four of these adult patients had coexpression with D816V. Three of the patients with V560G had advanced SM. These findings indicate that the V560G mutation could be used as a predictor of a severe type of mastocytosis.[14] The oldest study included in our review, by Büttner et al. could not find any mutation in children with mastocytosis, neither in exon 17 nor in exon 10. But they found a mutation in each adult patients with mastocytosis. They concluded that this data could give a

possible explanation for the divergent presentation and development of adult- versus childhood-onset mastocytosis. Namely that adult-onset mastocytosis is associated with an activation mutation and that childhood-onset mastocytosis is most likely a reactive process of an as yet unknown pathogenesis.[22] Nevertheless, this hypothesis seems now to be overruled. In more recent studies childhood-onset mastocytosis is seen as a clonal disease.[20] The group of Büttner and al. concluded that the detection of the D816V in all six adult patients suggests that it represents a feature of late-onset disease.[22] In the 3 studies that tested exon 10 of the c-KIT gene we could find 21 out of a total of 235 tested children carrying a mutation in exon 10 (**9%**). These 21 children were all carrying the M541L mutation, so no children were found who carried the V560G mutation.[4,14,22]

Only one study in our systematic review reported mutations in exon 13 of the c-KIT gene, namely the R634W mutation. Pollard et al. found this mutation in all of three genetic tested siblings with urticarial pigmentosa (**100%**). Because this is a rare mutation, it is unclear whether screening for this mutation in children with cutaneous mastocytosis would be beneficial. The R634W mutation has demonstrated sensitivity to tyrosine kinase inhibitors, including important implications about treatment options.[23]

The only study that examined mutations in exon 18 was conducted by the group of Wöhrl. They found a specific mutation, S849I, in 2 affected members of a family with 4 members affected by cutaneous mastocytosis (**50%**). They concluded that patients carrying this specific mutation are suspect to develop systemic mastocytosis in adulthood, and so have a tendency to incomplete resolution.[25] The fact that this mutation is only described in one article seems to indicate that this a very rare condition. Furthermore, this article is dealing with familial mastocytosis and inherited forms of mastocytosis are very rare. In conclusion, screening for mutations in exon 18 is experimental and is certainly not a standard procedure in mutation analysis in children with cutaneous mastocytosis. Furthermore this mutation has not been studied very well in mastocytosis and so further research on this particular mutation would be preferable.

Not all patients with mastocytosis expressed activating c-KIT mutations. In our study, 135 of 320 (**42.2%**) children had only wild-type c-KIT detectable.[4,17,19,20,24,27,28] This observation suggests that despite mutations in the c-KIT gene, also other genes may be involved in the onset of mastocytosis. For therapy the implication is that to cure mastocytosis, a combination of agents against c-KIT as well as to other genes is required.[20]

13 out of the 14 articles in this systematic review searched for mutations in the c-KIT gene. However, because no clear correlation between genotype and phenotype has been detected, other mutations seem to play a role in the development of cutaneous mastocytosis. Daley et al. focused on mutation in the gene for the IL4- receptor. Of the 9 genetic tested children in their study, 6 were carrying the Q576R-mutation in the IL4-R gene (**66.7%**). They compared the frequency of the IL4-R Q576R polymorphism to disease extent and prognosis. The polymorphism was more frequently found in patients with limited skin involvement. In conclusion, this study shows that IL4-R Q576R polymorphism in children with cutaneous mastocytosis plays a protective role in the limitation of mast cell numbers and thus may predict a better prognosis.[26] We must be careful to draw conclusions based on just one single study. Therefore further research on other genes than the c-KIT gene is highly required. The key question if a mutation in the IL4-R gene is really protective is a very interesting one. In the study by Daley et al. it seems that it is protective, but larger multi-centre studies are required to prove this hypothesis and a long time follow-up is necessary.

A recent article by Méni et al. (2018) a long term follow up of 53 children with cutaneous mastocytosis contained some interesting remarks. We discuss this article here because it is a very recent article (May 2018), not published yet at the time of our article selection process. Their main outcome was to

determine whether mutations in the c-KIT gene could predict evolution and clinical characteristics, very similar to our study outcomes. In this study, 21 patients of a total of 53 children with cutaneous mastocytosis showed a c-Kit mutation in exon 17 (39.6%), 25 patients a mutation the c-KIT gene other than exon 17 (47%) and 7 patients (13.2%) a wild-type genotype.[29] These results are in line with the results in our systematic review: we found a mutation in exon 17 in 110 of 344 (32%) genetic tested children and a wild-type genotype in 135 out of 320 tested children (42.2%), cfr. **Figure 4**. However, in their study only 3 children had a complete remission of mastocytosis. We must be aware, because it is possible, that the children in this study are partly included in our study too. The strength of this article is the 12 years duration of follow-up, whereas most studies included in our systematic review lack a long time follow-up.

**2. Remarks on tissue sampling**

Sampling of the tissue that undergoes mutation analysis differs between the selected studies. Mostly, DNA was collected on skin biopsies (10/14). Two studies retracted genetic material from blood cells. One study used bone marrow biopsies to conduct DNA analysis on. One study used both bone marrow and blood cells. Bone marrow lesional tissue has the highest sensitivity for detection of somatic *KIT* mutations due to the higher concentration of mast cell precursors and mature mast cells, and a bone marrow evaluation is the most useful means of evaluating for *KIT* mutations. While, analysis of peripheral blood cells is also possible, not all laboratories are able to sequence KIT from skin tissue. If the mutation is not detected in peripheral blood – which is common in patients with low mast cell burden – and there is a high index of suspicion due to compatible clinical symptoms, a bone marrow biopsy should be performed.[30] Most adults with CM will also exhibit involvement of bone marrow, therefore it is recommended to offer all adult patients a bone marrow biopsy. By contrast, in children with CM, a bone marrow biopsy is rarely required.[31,32]

**3. Limitations**

This study has several limitations. A first limitation concerns the lack of information especially in children. The ideal study is conducted only in children and follows these patients over time. However, many studies also include adult patients, which make it difficult to interpret results particularly about children with cutaneous mastocytosis. Sometimes, it was difficult to distinguish between children and adults. We must be aware to not making a fault in referral bias, like we do not always know the inclusion and exclusion criteria of each single study. Secondly, study sizes were often rather small. Many studies were case reports and described mutation analysis in at most dozen children. Only 3 of the 14 selected articles had more than 20 children in the study population. However, cutaneous mastocytosis is a rare disease and not in all cases a mutation analysis is conducted. This limitation can also explain why there is such a broad range in prevalence of a particular mutation. Therefore, replication and validation of current findings in sufficiently large studies will be necessary to draw conclusions. Another important consideration is that most studies only focuses on just a few mutations. That makes it difficult to compare between articles. The reasons why some authors described mutations in one exon and not in another has very divergent reasons and were usually not well specified. Furthermore, some of the articles were rather old. Half of the articles were published before 2010, only 7 articles after. Considering this, we should take into account that new possibilities of genetic testing could be more advanced and give more specific and detailed results. Finally, the search algorithm did not return many articles. The reason for this could be that cutaneous mastocytosis is a rather rare disease that usually regresses after puberty.

## CONCLUSION

While in adults with mastocytosis about 80% is associated with the D816V mutation in exon 17, in children a much broader variety of mutations occurs, whereof several are rarely observed in adults. We could not find significantly associations between specific mutations and prognosis, however interesting hypotheses have been made. From a clinical point of view, this systematic review makes these points clear:

1. The answer on the key question whether it is useful to conduct mutation analysis in children with cutaneous mastocytosis is still dubious. It is clear that in most situations, mutation analysis is not needed to make the diagnosis because mostly the clinical presentation is clear. Nevertheless, it is justified to do mutation analysis to decide if there will be a response to a treatment with tyrosine kinase inhibitors or not.
2. In this systematic review, it seems that there is no correlation between the presence of a particular mutation and clinical presentation. The remaining question is if the small associations that were found in a few studies are causal mutations of are rather found by chance and if these mutations are relevant in clinical practice or not.

Considering the limitations of this study, we believe that further genetic research in children with cutaneous mastocytosis is needed to clarify the role of specific mutations. Knowledge on specific mutations could be used in clinical practice to better adapt the treatment of pediatric mastocytosis in function of the chance to develop systemic mastocytosis.

## CONFLICTS OF INTEREST

None.

## FINANCIAL DISCLOSURE

None.

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**SUPPLEMENTAL DOCUMENTS**

**Supplemental document 1: guidelines for the use of local and general anesthetics in the hospital of Leuven, Belgium**

UZ LEUVEN

## RICHTLIJNEN VOOR ANESTHESIE BIJ MASTOCYTOSE (01-08-2014)

### 1. LOKALE ANESTHESIE

- Premedicatie (bij SM): cetirizine + ranitidine 1 uur vóór procedure
- Anestheticum bij voorkeur zonder adrenaline: Xylocard, Linisol, Marcaïne Hyperbaar, Scandonest 3% bupivacaine (Marcaïne), lidocaine (Linisol), xylocaïne
- Analgeticum: paracetamol (geen NSAID, codeïne of opioïden)

### 2. ALGEMENE ANESTHESIE

#### 2.1. PREMEDICATIE

| Electieve ingreep – ambulant via preoperatieve raadpleging anesthesie | | |
|---|---|---|
| | *Volwassenen (> 16 jaar)* | *Kinderen (<16 jaar)* |
| CM | Dag -2 t/m dag 1: cetirizine 10mg 1-2x/dag<br>ranitidine 300 mg | Dag -2 t/m dag 1: cetirizine 0.25 mg/kg<br>ranitidine 5mg/kg |
| SM | Dag -2 t/m dag 1: cetirizine 10mg 1-2x/dag<br>ranitidine 300 mg<br>montelukast 10 mg<br>Medrol 8 mg | Dag -2 t/m dag 1: cetirizine 0.25 mg/kg<br>ranitidine 5mg/kg<br>montelukast + Celestone<br>Dag 2 t/m dag 3: montelukast + Celestone<br>Montelukast: < 5 jaar: 4 mg; 5 -15 jaar: 5 mg; vanaf 15 jaar:10 mg<br>Celestone: 5-8 kg: 10 druppels; 8-10 kg: 15 druppels; 10-15 kg: 20 druppels; > 20 kg: 30 druppels |

| Urgente ingreep – in operatiezaal | | |
|---|---|---|
| | *Volwassenen (> 16 jaar)* | *Kinderen (<16 jaar)* |
| CM en SM | Dag 0: Phenergan IM 25mg 1 ampul<br>Zantac IV 50mg<br>Solumedrol IV 20 - 40 mg | Dag 0: Phenergan IM 1mg/kg<br>Zantac IV 5mg/kg<br>Solucortef IV 10 mg/kg |

CM= cutane mastocytose; SM= systemische mastocytose.

#### 2.2. ANESTHETICA

- Het individueel beleid wordt bepaald door de dienst anesthesie
- Toegelaten bij mastocytose:
  - Sedatie: benzodiazepines bv Dormicum (midazolam)
  - Hypnotica: gasanesthetica bv fluraanfamilie, etomidaat, propofol, ketamine
  - Myoplegica: cisatracurium (Nimbex), vecuronium (Norcuron), pancuronium (Pavulon)
  - Analgetica: fentanyl, sufentanil, remifentanil (Ultiva)

- Tegenaangewezen bij mastocytose:
  - Myoplegica: mivacurium (Mivacron), atracurium (Tracrium)
  - Analgetica: NSAID's, acetylsalicylzuur, opioïden, codeïne
  - Bèta –blokker

Deze UZ –richtlijnen werden opgesteld in samenwerking met:
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